



1. Plaintiffs' motion to remove deposition Exhibit 179 marked on March 15, 2006, from the Protective Order be and hereby is granted on the condition that the author's identifying information shall be redacted from the document and shall not be disclosed by counsel. Further, all information regarding other products shall be redacted from the document. Counsel shall agree on the form of the redacted document which is to be released from the Protective Order.

2. Plaintiffs' motion to remove a letter dated May 17, 2005 marked POE 03631554 through POE 03631571 from the Protective Order be and hereby is denied on procedural grounds and without prejudice and this document shall remain covered by the Protective Order.

3. Plaintiffs' motion to remove the document marked as Exhibit 181 on March 15, 2006 from the Protective Order be and hereby is granted on the condition that the identifying information of the author of Exhibit 179 shall be redacted from the document and shall not be disclosed by counsel. Further, all information regarding other products shall be redacted from the document. Counsel shall agree on the form of the redacted document which is to be released from the Protective Order.

4. ~~Decision is reversed on~~ Plaintiffs' motion to remove from the Protective Order the document from New Zealand marked as POE 0040516 through POE 00405178 is hereby granted. (See attached Letter Opinion and Exhibits).

5. Plaintiffs' motion to remove from the Protective Order the document bearing the Bates numbers POE00127898, POE127900 and POE127906 be and is hereby is granted.

6. Plaintiffs' motion to remove from the Protective Order the document marked as POE00477085 be and hereby is denied without prejudice.

7. Plaintiffs' motion to remove from the Protective Order the document marked as Bates No. POE03998220 to 221 be and hereby is denied.

8. Plaintiffs' motion to remove from the Protective Order the document marked as Bates No. POE07448272 to POE07448279 be and hereby is granted.

9. Release of documents pursuant to the terms and conditions of this Order be and hereby is stayed until August 24, 2007.

  
HONORABLE BRYAN D. GARRUTO, J.S.C.

# SUPERIOR COURT OF NEW JERSEY

CHAMBERS OF  
BRYAN D. GARRUTO  
JUDGE



MIDDLESEX COUNTY COURT HOUSE  
P.O. BOX 984  
NEW BRUNSWICK, NEW JERSEY 08903 - 0984

## MEMORANDUM OF DECISION ON MOTION

**TO:** Andres F. Alonso, Esq.  
Melanie Muhlstock, Esq.  
Parker Waichman Alonso Mark, LLP  
111 Great Neck Road, First Floor  
Great Neck, New York, 11021-5402

**RE:** *Brown v. Johnson & Johnson, et al.*, MID-L-5446-05 MT; This Opinion also applies to the following Docket Nos: MID-L-6209-05 MT, and MID-L-6227-05

**NATURE OF MOTION:** Motion to De-Designate Defendants' "Protected" Document Designations; The briefs pertaining to the within motion as well as the July 26, 2007 hearing are sealed.

Having carefully reviewed the moving papers, I have made the following  
**determination:**

This matter arises out of four of 309 mass tort cases centralized in the Superior Court of New Jersey, wherein the plaintiff allege personal injuries caused by use of the Ortho Evra® birth control patch. The Ortho Evra® birth control patch is manufactured by, and/or developed by, and/o patented, and/or trademarked by defendants Johnson & Johnson, Johnson & Johnson Pharmaceutical Research & Development, LLC, and/or Ortho-McNeil Pharmaceutical, Inc. ("the defendants" or "Johnson & Johnson").

On July 26, 2007, this Court determined whether "good cause" existed to maintain "protected designations" on documents that were produced by the defendants to the plaintiffs pursuant to an umbrella protective Order entered in the Multi-District Litigation in this matter. Pursuant to Comment 3 to R. 1:2-1, the Court is permitted to make "good cause" determinations

of the eight documents at issue *de novo*. In a closed hearing conducted on July 26, 2007, the Court made oral findings for seven of the eight documents. At that time, the Court reserved on the document entitled “Medicines Assessment Advisory Committee (MAAC) Report on the Evaluation of the Preclinical and Clinical Data of a New Medicine Application”, attached to the plaintiffs’ moving brief as “Exhibit G to the Muhlstock Certification”.

According to the plaintiffs, the findings of the MAAC Report are already public information and therefore do not consist of confidential, secret, or propriety information for which “good cause” exists to maintain a “protected” status. In addition, the plaintiffs assert that the MAAC Report should be declassified because it articulates many concerns regarding the safety of the Ortho Evra® birth control patch in relation to its application for approval in New Zealand. According to the plaintiffs, because the MAAC Report’s conclusion recommends not authorizing the Ortho Evra® product for approval, this document is important to the safety, health, and welfare of women currently taking the Ortho Evra® birth control patch as well as to physicians who prescribe the patch in the United States.

The defendants oppose the plaintiffs’ application for declassification on the notion that contrary to the plaintiffs’ assertions, the MAAC Report does contain trade secrets and other proprietary information. Defendants maintain that because this document is a clinical and pre-clinical evaluation from New Zealand’s MAAC [New Zealand’s equivalent of the FDA] and is not released to the general public upon request, it is considered confidential, commercial information. Defendants further assert that if this document is read alone and out of context, it would suggest that approval of the Ortho Evra® birth control patch in New Zealand has been denied permanently when the conclusions of the report merely suggest further study of outstanding issues. The defendants stress the importance of this document being read in its

appropriate context, which it feels would be better articulated in a court of law rather than a court of public opinion. Specifically, this document does not illustrate that despite the fact that New Zealand's MAAC did not recommend approval of the Ortho Evra® birth control patch, regulatory bodies of 79 other countries relied upon the same data when deciding to approve the product. At oral argument, counsel for Johnson & Johnson also expressed concerns that the MAAC Report contains trade secret-like material because it describes with particularity the formula for the patch. (Doc. De-designation Hr'g (Sealed), before J. Garruto, July 26, 2007, at Index No. 946 to 1020).

Absent a stipulated agreement between parties to designate documents as "protected", a court must decide whether there exists proper grounds to enter a protective order in a particular matter. Pursuant to *R. 4:10-3(g)*, a trial judge must determine whether "good cause" exists. While that rule does not define what constitutes "good cause", New Jersey law sets forth criteria a court can use to analyze documents. First, the court will determine whether the documents contain trade secrets, which will almost always be protected. If not, then the court will consider six other factors enunciated below.

In *Hammock by Hammock v. Hoffmann-LaRoche, Inc.*, the Supreme Court discussed the spectrum of evidence that may or may not be subject to a protective order suggesting a sliding scale of protected information. 142 *N.J.* 356, 380-81 (1995). First, the court will almost always protect trade secrets. Quoting Comment b of the *Restatement of Torts* § 757 (1939), the Supreme Court held that it would protect a trade secret, defined as:

any formula, pattern, device or compilation of information which is used in one's business, and which gives him an opportunity to obtain an advantage over competitors who do not know or use it. It may be a formula for a chemical compound, a process of manufacturing, treating or preserving materials, a pattern for a machine or other device, or a list of customers. *Hammock, supra*, 142 *N.J.* at 383 (referencing *Smith v. BIC Corp.*,

869 F.2d 194, 199 (3d Cir.1989) and (quoting *Restatement of Torts* § 757 comment b (1939)).

Conversely, the *Hammock* court found that the following information would not be protected as trade secrets: “information that is in the public domain or which has been ‘reverse engineered,’ i.e., garnered by beginning with the finished product and determining the process used to manufacture it” *Id.* (citing *Smith, supra*, 869 F.2d at 199-200).

Below the status of trade secrets is confidential and proprietary information.

“Confidential information and proprietary information are not entitled to the same level of protection from disclosure as trade secret information.” *Hammock, supra*, 142 N.J. at 383 (referencing *Littlejohn v. Bic Corp.*, 851 F.2d 673, 685 (3d Cir. 1988)). The *Hammock* Court adopted factors enunciated by the Third Circuit in *SI Handling Systems, Inc. v. Heisley*, 753 F.2d 1244, 1256 (3d Cir. 1985) to consider whether “good cause” existed to maintain the protection of a protective order:

(1) the extent to which the information is known outside of the owner’s business; (2) the extent to which it is known by employees and others involved in the owner’s business; (3) the extent of measures taken by the owner to guard the secrecy of the information; (4) the value of the information to the owner and to his competitors; (5) the amount of effort or money expended by the owner in developing the information; and (6) the ease or difficulty with which the information could be properly acquired or duplicated by others. *Hammock, supra*, 142 N.J. at 384. (citations omitted).

After considering the MAAC Report pursuant to the factors enunciated by the Supreme Court in *Hammock*, this court determines that no “good cause” exists to maintain the MAAC Report’s “protected status”, as it does not contain any trade secrets or other confidential/proprietary information. Defendants’ argument that the release of the MAAC Report will cause them harm if taken out of context is also unwarranted. The information contained in the MAAC Report is already in the public domain. Moreover, Johnson & Johnson has the financial resources

to respond to instances where the information contained is misapplied. The Court's reasoning and consideration of the *Hammock* factors is as follows:

**1. The extent to which the documents contain trade secrets.** *Hammock, supra*, 142 N.J. at 384.

The MAAC Report details pharmacotoxicological (pre-clinical) and clinical data related to the Ortho Evra® birth control patch. Defendants assert that “good cause” exists to maintain the “protected” status of the information contained in the MAAC Report because it consists of trade secret-like information, specifically the “recipe” for the patch. A close reading and comparison of the MAAC Report and information contained on the FDA website contradicts defendants’ assertion. The FDA lists similar – if not the exact – data as the MAAC Report on its website. *See* FDA, Ortho Evra® (norelgestromin/ethinyl estradiol) Information, <http://www.fda.gov/cder/drug/infopage/orthoevra/default.htm> (last checked July 26, 2007). (follow “Approved Labeling (9/20/2006)” hyperlink)(attached hereto as Exhibit A). Furthermore, in a document entitled “ORTHO EVRA® (norelgestromin/ethinyl estradiol) TRANSDERMAL SYSTEM”, the FDA provides the reader with a detailed description of the composition of the birth control patch, including specific instructions on how the drug is formulated as well as diagrams. *Available at* <http://www.fda.gov/cder/foi/label/2006/021180s0221bl.pdf> (last checked July 26, 2007)(attached hereto as Exhibit B). If the defendants’ primary concern is that the MAAC Report contains trade secret-like information on how to make the drug, their concern is misplaced, as that information is already in the public domain.

The defendants’ concerns that the testing data are trade secret-like information is also misplaced, as the FDA’s 62-page “Approved Labeling” report details the findings of numerous

studies, many of which are detailed in the MAAC Report. *See* Exhibit B, FDA, Ortho Evra® (norelgestromin/ethinyl estradiol) Information, PRECAUTIONS §§ “9. Interactions With Laboratory Tests”, at 24, “10. Carcinogenesis”, at 25, and “11. Pregnancy”, at 25 (detailing the findings of rat and rabbit studies), *available at* <http://www.fda.gov/cder/foi/label/2006/021180s0221bl.pdf>. Accordingly, on its face, the MAAC Report does not contain trade secret-like information. Furthermore, the defendants have not met their burden of proof that the document contains trade secret-like, as there is insufficient information on the record in support of its claim.

2. **“The extent to which the information is known outside of the owner’s business.”** *Hammock, supra*, 142 N.J. at 384.

At oral argument, counsel for Johnson & Johnson admitted that all the studies contained in the MAAC Report are publicly available, but that Johnson & Johnson’s concern was with the fact that the MAAC Report lays out a road map on how to develop the transdermal product. (Doc. De-designation Hr’g (Sealed), before J. Garruto, July 26, 2007, at Index No. 946 to 1020).

The information contained in the MAAC Report has been widely released to the general public, including the “recipe” for the drug. *See* Exhibit A, FDA, Ortho Evra® (norelgestromin/ethinyl estradiol) Information, *available at* <http://www.fda.gov/cder/drug/infopage/orthoevra/default.htm>. Although the precise wording of the MAAC Report may not already be in the public domain, the information contained therein can be obtained on the FDA website among others. The policy considerations enunciated in *Hammock* specifically aim to protect confidential or proprietary information, but not the specific categorization of such information in instances where it has already been released to the public. If the later were the case, parties could compile charts and graphs of information already in the

public domain and seek to have them “protected” on a copyright protection theory. However, this does not further the policy objectives intended by the Supreme Court in *Hammock*, which seek to protect businesses from the loss of competitive advantage.

3. **“The extent to which it is known by employees and others involved in the owner’s business”.** *Hammock, supra*, 142 N.J. at 384.

Counsel for defendants asserted at oral argument that her client took great pains to limit the access to the information contained in MAAC Report and that such information was kept securely within the company. (Doc. De-designation Hr’g (Sealed), before J. Garruto, July 26, 2007, at Index No. 946 to 1020). Perhaps the exact wording of the MAAC Report was kept confidential, but the information contained in the MAAC Report has been widely released to the general public in other forms.

4. **“The extent of measures taken by the owner to guard the secrecy of the information”.** *Hammock, supra*, 142 N.J. at 384.

As noted above, counsel for Johnson & Johnson indicated that her client kept the MAAC Report securely within the company and limited access to the document. Even if such is the case, the results of the numerous studies conducted in connection with the Ortho Evra® patch are ascertainable by scientists and the general public even if the MAAC Report itself is not. See Exhibit A, FDA, Ortho Evra® (norelgestromin/ethinyl estradiol) Information, <http://www.fda.gov/cder/drug/infopage/orthoevra/default.htm>.

5. **The “value of the information to the owner and to his competitors”.** *Hammock, supra*, 142 N.J. at 384.

Ortho-McNeil Pharmaceutical, Inc., whose parent company is Johnson & Johnson, owns the patents to the Ortho Evra® birth control patch, specifically U.S. Patent Number 5,876,746,

U.S. Patent Number 5,972,377, and U.S. Patent Number 6,071,531. (See Patent Assignment Abstract of Title for U.S. Patent Nos. 5,876,746; 5,972,377; and 6,071,531, attached hereto as Exhibit C). Not only is this information available on the internet, but also it is listed on the back of the box containing three individual Ortho Evra® (norelgestromin/ethinyl estradiol transdermal system) birth control patches. (See Photocopy of Ortho Evra® birth control patch box, attached hereto as Exhibit D). Accordingly, even if Johnson & Johnson's competitors knew the information contained in the MAAC Report, such information is protected by patent and Johnson & Johnson has a proper legal redress should that information be misappropriated.

**6. "The amount of effort or money expended by the owner in developing the information".** *Hammock, supra*, 142 N.J. at 384.

Johnson & Johnson has expended extensive time, money, and effort into developing the information contained in the MAAC Report. However, Johnson & Johnson has been compensated for these efforts by way of FDA-approval and the obtainment of federal patents and a federal trademark for the Ortho-Evra® birth control patch in the United States. It will not suffer a loss if the already-public information contained in the MAAC Report is released.

**7. "The ease or difficulty with which the information could be properly acquired or duplicated by others".** *Hammock, supra*, 142 N.J. at 384.

The results of the studies contained in this report are not secret. Pursuant to the laws of the United States protecting patents and trademarks, Johnson & Johnson has a form of legal redress should a party engage in the unauthorized duplication of the information contained in the MAAC Report.

For the foregoing reasons, plaintiffs' motion to declassify the MAAC Report is **granted**.  
The MAAC Report is attached to this Letter Opinion as Exhibit E. This Order is effective 14 days after the date hereof so that counsel for the defendants may have time to object.

**DATED:** August 10, 2007

  
**Hon. Bryan D. Garruto, J.S.C.**

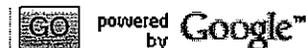
# **Court's Exhibit A**



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## Ortho Evra (norelgestromin/ethinyl estradiol) Information

- [Approved Labeling](#)  (9/20/2006)
- [Approval Letter](#)  (9/20/2006)
- [Questions and Answers](#) (9/20/2006)
- [Patient Information Sheet](#) (12/13/2005)

### Historical Information

- [FDA News](#)
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FDA/Center for Drug Evaluation and Research

# **Court's Exhibit B**

**ORTHO EVRA<sup>®</sup>**  
**(norelgestromin / ethinyl estradiol**  
**TRANSDERMAL SYSTEM)**

**Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.**

**Rx only**

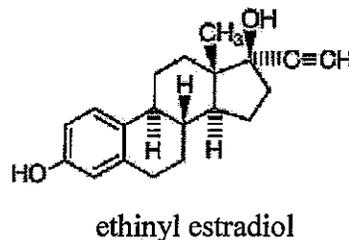
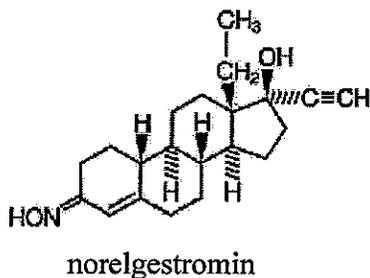
**DESCRIPTION**

ORTHO EVRA<sup>®</sup> is a combination transdermal contraceptive patch with a contact surface area of 20 cm<sup>2</sup>. It contains 6.00 mg norelgestromin (NGMN) and 0.75 mg ethinyl estradiol (EE). Systemic exposures (as measured by area under the curve [AUC] and steady state concentration [C<sub>ss</sub>]) of NGMN and EE during use of ORTHO EVRA<sup>®</sup> are higher and peak concentrations (C<sub>max</sub>) are lower than those produced by an oral contraceptive containing norgestimate 250 µg / EE 35 µg. (See BOLDED WARNING; CLINICAL PHARMACOLOGY, Transdermal versus Oral Contraceptives).

ORTHO EVRA<sup>®</sup> is a thin, matrix-type transdermal contraceptive patch consisting of three layers. The backing layer is composed of a beige flexible film consisting of a low-density pigmented polyethylene outer layer and a polyester inner layer. It provides structural support and protects the middle adhesive layer from the environment. The middle layer contains polyisobutylene/polybutene adhesive, crospovidone, non-woven polyester fabric and lauryl lactate as inactive components. The active components in this layer are the hormones, norelgestromin and ethinyl estradiol. The third layer is the release liner, which protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyethylene terephthalate (PET) film with a polydimethylsiloxane coating on the side that is in contact with the middle adhesive layer.

The outside of the backing layer is heat-stamped "ORTHO EVRA<sup>®</sup>."

The structural formulas of the components are:



**Molecular weight, norelgestromin: 327.47**

**Molecular weight, ethinyl estradiol: 296.41**

**Chemical name for norelgestromin: 18, 19-dinorpregn-4-en-20-yn-3-one, 13-ethyl- 17-hydroxy-, 3-oxime, (17 $\alpha$ )**

**Chemical name for ethinyl estradiol: 19-Norpregna-1, 3, 5 (10)-trien-20-yne-3, 17-diol, (17 $\alpha$ )**

## **CLINICAL PHARMACOLOGY**

### **Pharmacodynamics**

Norelgestromin is the active progestin largely responsible for the progestational activity that occurs in women following application of ORTHO EVRA<sup>®</sup>. Norelgestromin is also the primary active metabolite produced following oral administration of norgestimate (NGM), the progestin component of the oral contraceptive products ORTHO-CYCLEN<sup>®</sup> and ORTHO TRI-CYCLEN<sup>®</sup>.

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

Receptor and human sex hormone-binding globulin (SHBG) binding studies, as well as studies in animals and humans, have shown that both NGM and NGMN exhibit high progestational activity with minimal intrinsic androgenicity<sup>90-93</sup>. Transdermally-administered norelgestromin, in combination with ethinyl estradiol, does not counteract the estrogen-induced increases in SHBG, resulting in lower levels of free testosterone in serum compared to baseline.

One clinical trial assessed the return of hypothalamic-pituitary-ovarian axis function post-therapy and found that FSH, LH, and Estradiol mean values, though suppressed during therapy, returned to near baseline values during the 6 weeks post therapy.

### **Pharmacokinetics**

#### **Absorption**

Following a single application of ORTHO EVRA<sup>®</sup>, both NGMN and EE reach a plateau by approximately 48 hours. Pooled data from the 3 clinical studies have demonstrated that steady state is reached within 2 weeks of application. The mean steady state C<sub>ss</sub> concentrations ranged from 0.305 –1.53 ng/mL for NGMN and from 11.2 - 137 pg/mL for EE.

Absorption of NGMN and EE following application of ORTHO EVRA<sup>®</sup> to the buttock, upper outer arm, abdomen and upper torso (excluding breast) was examined.

While absorption from the abdomen was slightly lower than from other sites, absorption from these anatomic sites was considered to be therapeutically equivalent.

The mean (%CV) pharmacokinetic parameters  $C_{ss}$  and  $AUC_{0-168}$  for NGMN and EE following a single buttock application of ORTHO EVRA<sup>®</sup> are summarized in Table 1.

In multiple dose studies,  $AUC_{0-168}$  for NGMN and EE was found to increase over time (Table 1). In a three-cycle study, these pharmacokinetic parameters reached steady-state conditions during Cycle 3 (Figures 1 and 2). Upon removal of the patch, serum levels of EE and NGMN reach very low or non-measurable levels within 3 days.

Table 1: Mean (%CV\*) Pharmacokinetic Parameters of Norelgestromin (NGMN) and Ethinyl Estradiol (EE) Following 3 Consecutive Cycles of ORTHO EVRA<sup>®</sup> Wear on the Buttock

Analyte	Parameter	Cycle 1 Week 1	Cycle 3 Week 1	Cycle 3 Week 2	Cycle 3 Week 3
NGMN	$C_{ss}$ (ng/mL)	0.70 (39.4)	0.70 (41.8)	0.80 (28.7)	0.70 (45.3)
	$AUC_{0-168}$ (ng.h/mL)	107 (44.2)	105 (43.2)	132 (43.4)	120 (43.9)
	$t_{1/2}$ (h)	nc	nc	nc	32.1 (40.3)
EE	$C_{ss}$ (pg/mL)	46.4 (38.5)	47.6 (36.4)	59.0 (42.5)	49.6 (54.4)
	$AUC_{0-168}$ (pg.h/mL)	6796 (39.3)	7160 (40.4)	10054 (41.8)	8840 (58.6)
	$t_{1/2}$ (h)	nc	nc	nc	21.0 (43.2)

nc = not calculated, \*%CV is % of Coefficient of variation = 100 (standard deviation/mean)

Figure 1: Mean Serum NGMN Concentrations (ng/mL) in Healthy Female Volunteers Following Application of ORTHO EVRA<sup>®</sup> on the Buttock for Three Consecutive Cycles (Vertical arrow indicates time of patch removal)

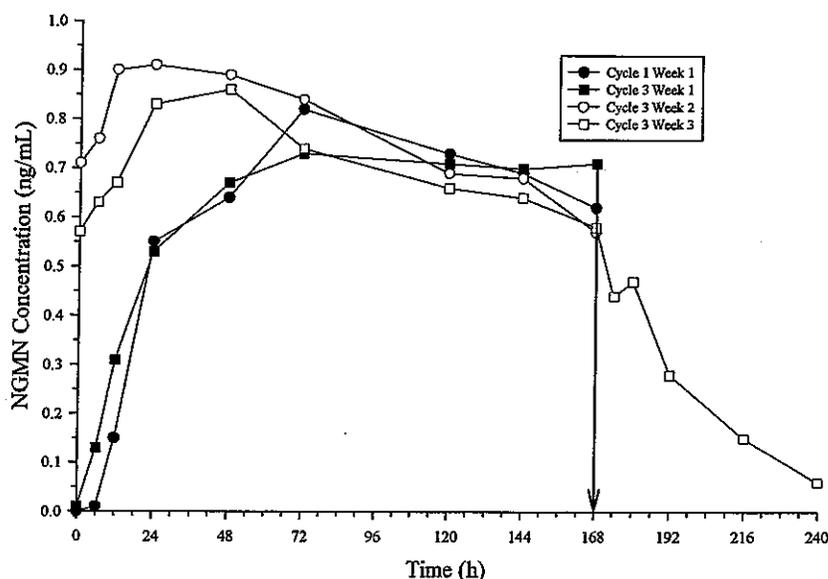
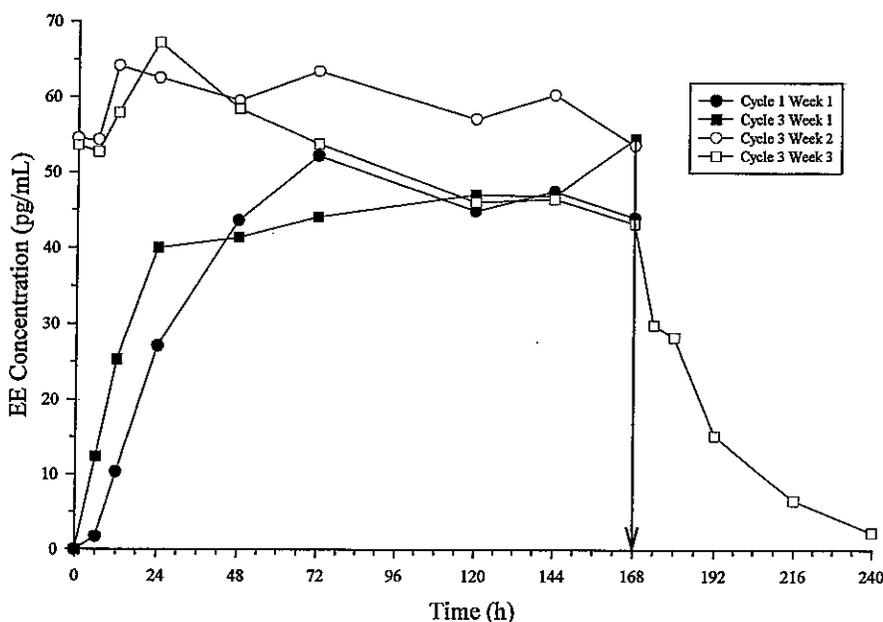


Figure 2: Mean Serum EE Concentrations (pg/mL) in Healthy Female Volunteers Following Application of ORTHO EVRA® on the Buttock for Three Consecutive Cycles (Vertical arrow indicates time of patch removal.)



The absorption of NGMN and EE following application of ORTHO EVRA® was studied under conditions encountered in a health club (sauna, whirlpool and treadmill) and in a cold water bath. The results indicated that for NGMN there were no significant treatment effects on  $C_{ss}$  or AUC when compared to normal wear. For EE, increased exposures were observed due to sauna, whirlpool and treadmill. There was no significant effect of cold water on these parameters.

Results from a study of consecutive ORTHO EVRA® wear for 7 days and 10 days indicated that serum concentrations of NGMN and EE dropped slightly during the first 6 hours after the patch replacement, and recovered within 12 hours. By Day 10 of patch administration, both NGMN and EE concentrations had decreased by approximately 25% when compared to Day 7 concentrations.

### Metabolism

Since ORTHO EVRA® is applied transdermally, first-pass metabolism (via the gastrointestinal tract and/or liver) of NGMN and EE that would be expected with oral administration is avoided. Hepatic metabolism of NGMN occurs and metabolites include norgestrel, which is highly bound to SHBG, and various hydroxylated and conjugated metabolites. Ethinyl estradiol is also metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.

## Distribution

NGMN and norgestrel (a serum metabolite of NGMN) are highly bound (>97%) to serum proteins. NGMN is bound to albumin and not to SHBG, while norgestrel is bound primarily to SHBG, which limits its biological activity. Ethinyl estradiol is extensively bound to serum albumin and induces an increase in the serum concentrations of SHBG (See CLINICAL PHARMACOLOGY, Transdermal versus Oral Contraceptives, Table 3).

## Elimination

Following removal of patches, the elimination kinetics of NGMN and EE were consistent for all studies with half-life values of approximately 28 hours and 17 hours, respectively. The metabolites of NGMN and EE are eliminated by renal and fecal pathways.

## Transdermal versus Oral Contraceptives

The ORTHO EVRA<sup>®</sup> transdermal patch was designed to deliver EE and NGMN over a seven-day period while oral contraceptives (containing NGM 250 µg / EE 35 µg) are administered on a daily basis. Figures 3 and 4 present mean pharmacokinetic (PK) profiles for EE and NGMN following administration of an oral contraceptive (containing NGM 250 µg / EE 35 µg) compared to the 7-day transdermal ORTHO EVRA<sup>®</sup> patch (containing NGMN 6.0 mg / EE 0.75 mg) during cycle 2 in 32 healthy female volunteers.

Figure 3: Mean Serum Concentration-Time Profiles of NGMN Following Once-Daily Administration of an Oral Contraceptive for 2 cycles or Application of ORTHO EVRA<sup>®</sup> for 2 cycles to the Buttock in Healthy Female Volunteers. [Oral contraceptive: Cycle 2, Days 15-21, ORTHO EVRA<sup>®</sup> Cycle 2, week 3]

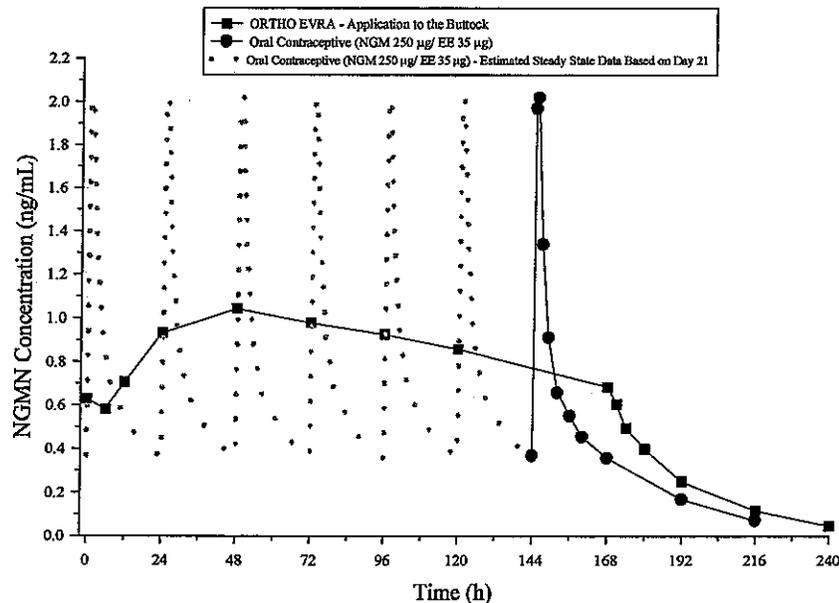


Figure 4: Mean Serum Concentration-Time Profiles of EE Following Once-Daily Administration of an Oral Contraceptive for 2 cycles or Application of ORTHO EVRA® for 2 cycles to the Buttock in Healthy Female Volunteers. [Oral contraceptive: Cycle 2, Days 15-21, ORTHO EVRA® Cycle 2, week 3]

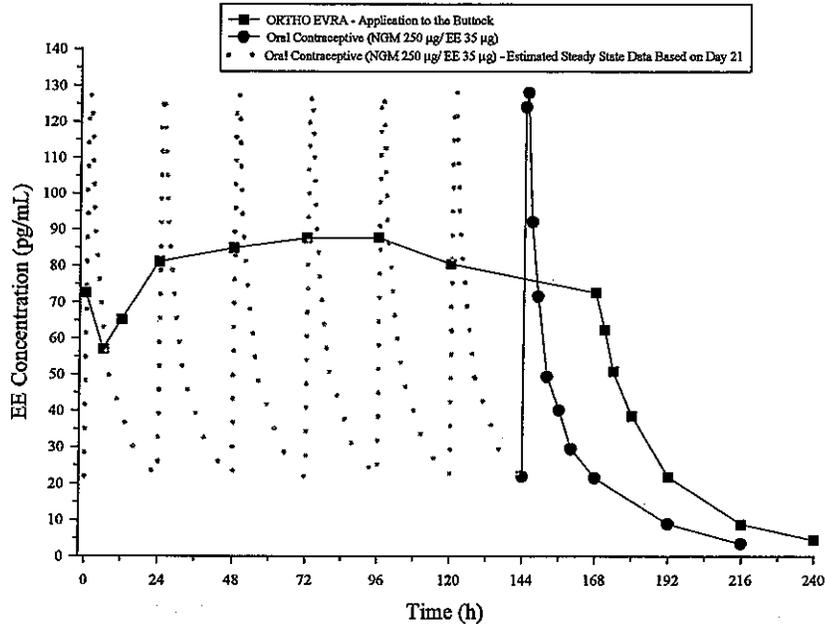


Table 2 provides the mean (%CV) for NGMN and EE pharmacokinetic (PK) parameters.

Table 2: Mean (%CV) NGMN and EE Steady State Pharmacokinetic Parameters Following Application of ORTHO EVRA® and Once-daily Administration of an Oral Contraceptive (containing NGM 250 µg / EE 35 µg) in Healthy Female Volunteers

Parameter	ORTHO EVRA <sup>e</sup>	ORAL CONTRACEPTIVE <sup>d</sup>
<b>NGMN<sup>a</sup></b>		
$C_{max}$ (ng/mL)	1.12 (33.6)	2.16 (25.2)
$AUC_{0-168}$ (ng.h/mL)	145 (36.8)	123 (30.2) <sup>b</sup>
$C_{ss}$ (ng/mL)	0.888 (36.6)	0.732 (30.2) <sup>c</sup>
<b>EE</b>		
$C_{max}$ (pg/mL)	97.4 (31.6)	133 (27.7)
$AUC_{0-168}$ (pg.h/mL)	12,971 (33.1)	8,281 (26.9) <sup>b</sup>
$C_{ss}$ (pg/mL)	80.0 (33.5)	49.3 (26.9) <sup>c</sup>

<sup>a</sup> NGM is rapidly metabolized to NGMN following oral administration

<sup>b</sup> Average weekly exposure, calculated as  $AUC_{24} \times 7$

<sup>c</sup>  $C_{avg}$

<sup>d</sup> Cycle 2, Day 21

<sup>e</sup> Cycle 2, Week 3

In general, overall exposure for NGMN and EE ( $AUC$  and  $C_{ss}$ ) was higher in subjects treated with ORTHO EVRA® for both Cycle 1 and Cycle 2, compared to that for the oral contraceptive, while  $C_{max}$  values were higher in subjects administered the oral

contraceptive. Under steady-state conditions,  $AUC_{0-168}$  and  $C_{ss}$  for EE were approximately 55% and 60% higher, respectively, for the transdermal patch, and the  $C_{max}$  was about 35% higher for the oral contraceptive, respectively. Inter-subject variability (%CV) for the PK parameters following delivery from ORTHO EVRA<sup>®</sup> 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.

In Table 3, percent change in concentrations (%CV) of markers of systemic estrogenic activity (Sex Hormone Binding Globulin [SHBG] and Corticosteroid Binding Globulin [CBG]) from Cycle 1 Day 1 to Cycle 1 Day 22 is presented. Percent change in SHBG concentrations was higher for ORTHO EVRA<sup>®</sup> users compared to women taking the oral contraceptive; percent change in CBG concentrations were similar for ORTHO EVRA<sup>®</sup> and oral contraceptive users. Within each group, the absolute values for SHBG were similar for Cycle 1, Day 22 and Cycle 2, Day 22.

Table 3: Mean Percent Change (%CV) in SHBG and CBG Concentrations Following Once-daily Administration of an Oral Contraceptive (containing NGM 250 µg / EE 35 µg) for One Cycle and Application of ORTHO EVRA<sup>®</sup> for One Cycle in Healthy Female Volunteers

Parameter	ORTHO EVRA <sup>®</sup>	ORAL CONTRACEPTIVE
	(% change from Day 1 to Day 22)	(% change from Day 1 to Day 22)
SHBG	334 (39.3)	200 (43.2)
CBG	153 (40.2)	157 (33.4)

### Special Populations

#### Effects of Age, Body Weight, Body Surface Area and Race:

The effects of age, body weight, body surface area and race on the pharmacokinetics of NGMN and EE were evaluated in 230 healthy women from nine pharmacokinetic studies of single 7-day applications of ORTHO EVRA<sup>®</sup>. For both NGMN and EE, increasing age, body weight and body surface area each were associated with slight decreases in  $C_{ss}$  and AUC values. However, only a small fraction (10-25%) of the overall variability in the pharmacokinetics of NGMN and EE following application of ORTHO EVRA<sup>®</sup> may be associated with any or all of the above demographic parameters. There was no significant effect of race with respect to Caucasians, Hispanics and Blacks.

### **Renal and Hepatic Impairment**

No formal studies were conducted with ORTHO EVRA<sup>®</sup> to evaluate the pharmacokinetics, safety, and efficacy in women with renal or hepatic impairment. Steroid hormones may be poorly metabolized in patients with impaired liver function (see PRECAUTIONS).

### **Drug Interactions**

The metabolism of hormonal contraceptives may be influenced by various drugs. Of potential clinical importance are drugs that cause the induction of enzymes that are responsible for the degradation of estrogens and progestins, and drugs that interrupt entero-hepatic recirculation of estrogen (e.g. certain antibiotics)<sup>72</sup>.

The proposed mechanism of interaction of antibiotics is different from that of liver enzyme-inducing drugs. Literature suggests possible interactions with the concomitant use of hormonal contraceptives and ampicillin or tetracycline. In a pharmacokinetic drug interaction study, oral administration of tetracycline HCl, 500 mg q.i.d. for 3 days prior to and 7 days during wear of ORTHO EVRA<sup>®</sup> did not significantly affect the pharmacokinetics of NGMN or EE.

The major target for enzyme inducers is the hepatic microsomal estrogen-2-hydroxylase (cytochrome P450 3A4)<sup>99</sup>. See also PRECAUTIONS, Drug Interactions.

### **Patch Adhesion**

In the clinical trials with ORTHO EVRA<sup>®</sup>, approximately 2% of the cumulative number of patches completely detached. The proportion of subjects with at least 1 patch that completely detached ranged from 2% to 6%, with a reduction from Cycle 1 (6%) to Cycle 13 (2%). For instructions on how to manage detachment of patches, refer to the DOSAGE AND ADMINISTRATION section.

### **INDICATIONS AND USAGE**

ORTHO EVRA<sup>®</sup> is indicated for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception.

The pharmacokinetic profile for the ORTHO EVRA<sup>®</sup> transdermal patch is different from that of an oral contraceptive. Healthcare professionals should balance the higher estrogen exposure and the possible increased risk of venous thromboembolism with ORTHO EVRA<sup>®</sup> against the chance of pregnancy if a contraceptive pill is not taken daily. (See BOLDED WARNING; WARNINGS; CLINICAL PHARMACOLOGY, Transdermal versus Oral Contraceptives).

Like oral contraceptives, ORTHO EVRA<sup>®</sup> is highly effective if used as recommended in this label.

In 3 large clinical trials in North America, Europe and South Africa, 3,330 women (ages 18-45) completed 22,155 cycles of ORTHO EVRA<sup>®</sup> use, pregnancy rates were approximately 1 per 100 women-years of ORTHO EVRA<sup>®</sup> use. The racial distribution was 91% Caucasian, 4.9% Black, 1.6% Asian, and 2.4% Other.

With respect to weight, 5 of the 15 pregnancies reported with ORTHO EVRA<sup>®</sup> use were among women with a baseline body weight  $\geq$ 198 lbs. (90kg), which constituted <3% of the study population. The greater proportion of pregnancies among women at or above 198 lbs. was statistically significant and suggests that ORTHO EVRA<sup>®</sup> may be less effective in these women.

Health Care Professionals who consider ORTHO EVRA<sup>®</sup> for women at or above 198 lbs. should discuss the patient's individual needs in choosing the most appropriate contraceptive option.

Table 4 lists the accidental pregnancy rates for users of various methods of contraception. The efficacy of these contraceptive methods, except sterilization, IUD, and Norplant depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

Table 4: Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year, United States.

Method (1)	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at One Year <sup>3</sup>
	Typical Use <sup>1</sup> (2)	Perfect Use <sup>2</sup> (3)	(4)
Chance <sup>4</sup>	85	85	
Spermicides <sup>5</sup>	26	6	40
Periodic abstinence	25		63
Calendar		9	
Ovulation Method		3	
Sympto-Thermal <sup>6</sup>		2	
Post-Ovulation		1	
Cap <sup>7</sup>			
Parous Women	40	26	42
Nulliparous Women	20	9	56
Sponge			
Parous Women	40	20	42
Nulliparous Women	20	9	56
Diaphragm <sup>7</sup>	20	6	56
Withdrawal	19	4	
Condom <sup>8</sup>			
Female (Reality®)	21	5	56
Male	14	3	61
Pill	5		71
Progestin Only		0.5	
Combined		0.1	
IUD			
Progesterone T	2.0	1.5	81
Copper T380A	0.8	0.6	78
LNg 20	0.1	0.1	81
Depo-Provera®	0.3	0.3	70
Norplant® and Norplant-2®	0.05	0.05	88
Female Sterilization	0.5	0.5	100
Male Sterilization	0.15	0.10	100

Hatcher et al, 1998, Ref. # 1.

### Emergency Contraceptive Pills:

Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.<sup>9</sup>

### Lactational Amenorrhea Method:

LAM is highly effective, *temporary* method of contraception.<sup>10</sup>

Source: Trussell J, Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Kowal D, Guest F, Contraceptive Technology: Seventeenth Revised Edition. New York NY: Irvington Publishers, 1998.

<sup>1</sup> Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

- 2 Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
- 3 Among couples attempting to avoid pregnancy, the percentage who continue to use a method for one year.
- 4 The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within one year. This estimate was lowered slightly (to 85%) to represent the percent who would become pregnant within one year among women now relying on reversible methods of contraception if they abandoned contraception altogether.
- 5 Foams, creams, gels, vaginal suppositories, and vaginal film.
- 6 Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.
- 7 With spermicidal cream or jelly.
- 8 Without spermicides.
- 9 The treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The Food and Drug Administration has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral<sup>®</sup> (1 dose is 2 white pills), Alesse<sup>®</sup> (1 dose is 5 pink pills), Nordette<sup>®</sup> or Levlen<sup>®</sup> (1 dose is 2 light-orange pills), Lo/Ovral<sup>®</sup> (1 dose is 4 white pills), Triphasil<sup>®</sup> or Tri-Levlen<sup>®</sup> (1 dose is 4 yellow pills).
- 10 However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches six months of age.

***ORTHO EVRA<sup>®</sup> has not been studied for and is not indicated for use in emergency contraception.***

#### **CONTRAINDICATIONS**

ORTHO EVRA<sup>®</sup> should not be used in women who currently have the following conditions:

- Thrombophlebitis, thromboembolic disorders
- A past history of deep vein thrombophlebitis or thromboembolic disorders
- Cerebrovascular or coronary artery disease (current or past history)

- Valvular heart disease with complications<sup>103</sup>
- Severe hypertension<sup>103</sup>
- Diabetes with vascular involvement<sup>103</sup>
- Headaches with focal neurological symptoms
- Major surgery with prolonged immobilization
- Known or suspected carcinoma of the breast or personal history of breast cancer
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use
- Acute or chronic hepatocellular disease with abnormal liver function<sup>103</sup>
- Hepatic adenomas or carcinomas
- Known or suspected pregnancy
- Hypersensitivity to any component of this product

#### **WARNINGS**

**Cigarette smoking increases the risk of serious cardiovascular side effects from hormonal contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use hormonal contraceptives, including ORTHO EVRA<sup>®</sup>, should be strongly advised not to smoke.**

The pharmacokinetic (PK) profile for the ORTHO EVRA<sup>®</sup> patch is different from the PK profile for oral contraceptives in that it has higher steady state concentrations and lower peak concentrations. AUC and average concentration at steady state for ethinyl estradiol (EE) are approximately 60% higher in women using ORTHO EVRA<sup>®</sup> compared with women using an oral contraceptive containing EE 35 µg. In contrast, peak concentrations for EE are approximately 25% lower in women using ORTHO EVRA<sup>®</sup>. Inter-subject variability results in increased exposure to EE in some women using either ORTHO EVRA<sup>®</sup> or oral contraceptives. However, inter-subject variability in women using ORTHO EVRA<sup>®</sup> is higher. It is not known whether there are changes in the risk of serious adverse events based on the differences in pharmacokinetic profiles of EE in women using ORTHO EVRA<sup>®</sup> compared with women using oral contraceptives containing 35 µg of EE. Increased estrogen exposure may increase the risk of adverse events, including venous

**thromboembolism. (See CLINICAL PHARMACOLOGY, Transdermal versus Oral Contraceptives).**

The risk of venous thromboembolism (VTE) in users of ORTHO EVRA<sup>®</sup> compared to users of oral contraceptives containing norgestimate and 35 mcg of EE was assessed in two epidemiological studies with a nested case control design conducted in the U.S. in women from ages 15 to 44 years. Both studies were conducted using electronic health care claims data. One of these studies<sup>107</sup>, which also included patient chart review, found an increased risk of VTEs for current users of ORTHO EVRA<sup>®</sup> compared to current users of the oral contraceptives. The odds ratio for current users in this study was 2.4 (95% CI 1.1 – 5.5). The other study<sup>108</sup> did not find an increase in risk of VTEs for current users of ORTHO EVRA<sup>®</sup> (odds ratio 0.9 [95% CI 0.5 - 1.6]).

In 3 large clinical trials (N= 3,330 with 1,704 women-years of exposure), one case of non-fatal pulmonary embolism occurred during ORTHO EVRA<sup>®</sup> use, and one case of post-operative non-fatal pulmonary embolism was reported following ORTHO EVRA<sup>®</sup> use.

ORTHO EVRA<sup>®</sup> and other contraceptives that contain both an estrogen and a progestin are called combination hormonal contraceptives. As with any combination hormonal contraceptive, the clinician should be alert to the earliest manifestations of thromboembolic disorders (thrombophlebitis, VTE including pulmonary embolism, cerebrovascular disorders, and retinal thrombosis). Should any of these occur or be suspected, ORTHO EVRA<sup>®</sup> should be discontinued immediately.

Practitioners prescribing ORTHO EVRA<sup>®</sup> should be familiar with the following information relating to risks:

The use of combination hormonal contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes.

The information that follows in this section of the package insert is principally based on studies carried out in women who used combination oral contraceptives with higher formulations of estrogens and progestins than those in common use today. The effect of long-term use of combination hormonal contraceptives with lower doses of both estrogen and progestin administered by any route remains to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a ratio of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the *difference* in the incidence of disease between hormonal contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population (adapted from refs. 2 and 3 with the author's permission). For further information, the reader is referred to a text on epidemiological methods.

## **1. Thromboembolic Disorders and Other Vascular Problems**

### **a. Thromboembolism**

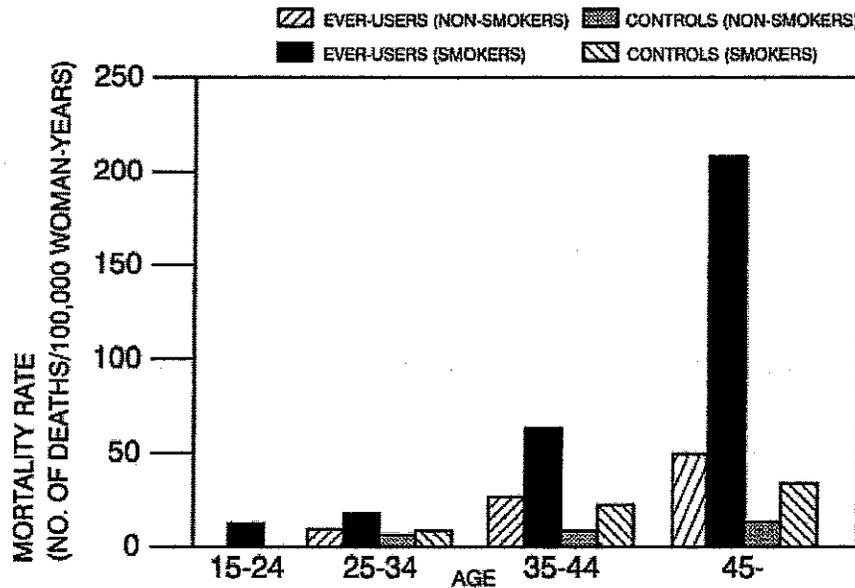
An increased risk of thromboembolic and thrombotic disease associated with the use of hormonal contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease<sup>2,3,19-24</sup>. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization<sup>25</sup>. The risk of thromboembolic disease associated with hormonal contraceptives is not related to length of use and disappears after hormonal contraceptive use is stopped<sup>2</sup>. A two- to four-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of hormonal contraceptives<sup>9,26</sup>. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions<sup>9,26</sup>. If feasible, hormonal contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, hormonal contraceptives should be started no earlier than four weeks after delivery in women who elect not to breast-feed.

### **b. Myocardial Infarction**

An increased risk of myocardial infarction has been attributed to hormonal contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current hormonal contraceptive users has been estimated to be two to six<sup>4-10</sup> compared to non-users. The risk is very low under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases<sup>11</sup>. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers, especially in those 35 years of age and older among women who use oral contraceptives. (See [Figure 5](#))

Figure 5: Circulatory Disease Mortality Rates Per 100,000 Women-Years by Age, Smoking Status and Oral Contraceptive Use



Hormonal contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity<sup>13</sup>. In particular, some progestins are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism<sup>14-18</sup>. Hormonal contraceptives have been shown to increase blood pressure among some users (see [Section 9 in WARNINGS](#)). Similar effects on risk factors have been associated with an increased risk of heart disease. Hormonal contraceptives, including ORTHO EVRA<sup>®</sup>, must be used with caution in women with cardiovascular disease risk factors.

Norgestimate and norelgestromin have minimal androgenic activity (see [CLINICAL PHARMACOLOGY](#)). There is some evidence that the risk of myocardial infarction associated with hormonal contraceptives is lower when the progestin has minimal androgenic activity than when the activity is greater<sup>97</sup>.

### c. Cerebrovascular Diseases

Hormonal contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes),

although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, and smoking interacted to increase the risk of stroke<sup>27-29</sup>.

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension<sup>30</sup>. The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used hormonal contraceptives, 2.6 for smokers who did not use hormonal contraceptives, 7.6 for smokers who used hormonal contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension<sup>30</sup>. The attributable risk is also greater in older women<sup>3</sup>.

#### d. Dose-Related Risk of Vascular Disease From Hormonal Contraceptives

A positive association has been observed between the amount of estrogen and progestin in hormonal contraceptives and the risk of vascular disease<sup>31-33</sup>. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents<sup>14-16</sup>. A decline in serum high-density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of a hormonal contraceptive depends on a balance achieved between doses of estrogen and progestin and the activity of the progestin used in the contraceptives. The activity and amount of both hormones should be considered in the choice of a hormonal contraceptive.

#### e. Persistence of Risk of Vascular Disease

There are two studies that have shown persistence of risk of vascular disease for ever-users of combination hormonal contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing combination hormonal contraceptives persists for at least 9 years for women 40-49 years who had used combination hormonal contraceptives for five or more years, but this increased risk was not demonstrated in other age groups<sup>8</sup>. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of combination hormonal contraceptives, although excess risk was very small<sup>34</sup>. However, both studies were performed with combination hormonal contraceptive formulations containing 50 micrograms or higher of estrogens.

## 2. Estimates of Mortality From Combination Hormonal Contraceptive Use

One study gathered data from a variety of sources that have estimated the mortality rate associated with different methods of contraception at different ages (Table 5). These estimates include the combined risk of death associated with contraceptive

methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of combination oral contraceptive users 35 and older who smoke, and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth.

The observation of a possible increase in risk of mortality with age for combination oral contraceptive users is based on data gathered in the 1970's but not reported until 1983<sup>35</sup>. Current clinical recommendation involves the use of lower estrogen dose formulations and a careful consideration of risk factors. In 1989, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the use of combination hormonal contraceptives in women 40 years of age and over. The Committee concluded that although cardiovascular disease risks may be increased with combination hormonal contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures that may be necessary if such women do not have access to effective and acceptable means of contraception. The Committee recommended that the benefits of low-dose combination hormonal contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks<sup>36, 37</sup>.

Although the data are mainly obtained with oral contraceptives, this is likely to apply to ORTHO EVRA<sup>®</sup> as well. Women of all ages who use combination hormonal contraceptives, should use the lowest possible dose formulation that is effective and meets the individual patient needs.

Table 5: Annual Number of Birth-Related or Method-Related Deaths Associated With Control of Fertility Per 100,000 Non-Sterile Women, by Fertility Control Method According to Age

Method of control and outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives, non-smoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives, smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

\*Deaths are birth-related

\*\*Deaths are method-related

Adapted from H.W. Ory, ref. # 35.

### **3. Carcinoma of the Reproductive Organs and Breasts**

Numerous epidemiological studies give conflicting reports on the relationship between breast cancer and COC use. The risk of having breast cancer diagnosed may be slightly increased among current and recent users of combination oral contraceptives. However, this excess risk appears to decrease over time after COC discontinuation and by 10 years after cessation the increased risk disappears. Some studies report an increased risk with duration of use while other studies do not and no consistent relationships have been found with dose or type of steroid. Some studies have found a small increase in risk for women who first use COCs before age 20. Most studies show a similar pattern of risk with COC use regardless of a woman's reproductive history or her family breast cancer history.

In addition, breast cancers diagnosed in current or ever oral contraceptive users may be less clinically advanced than in never-users.

Women who currently have or have had breast cancer should not use hormonal contraceptives because breast cancer is usually a hormonally sensitive tumor.

Some studies suggest that combination oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women<sup>45-48</sup>. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between oral contraceptive use and breast and cervical cancers, a cause-and-effect relationship has not been established. It is not known whether ORTHO EVRA<sup>®</sup> is distinct from oral contraceptives with regard to the above statements.

### **4. Hepatic Neoplasia**

Benign hepatic adenomas are associated with hormonal contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use, especially with hormonal contraceptives containing 50 micrograms or more of estrogen<sup>49</sup>. Rupture of benign, hepatic adenomas may cause death through intra-abdominal hemorrhage<sup>50,51</sup>.

Studies from Britain and the US have shown an increased risk of developing hepatocellular carcinoma in long term ( $\geq 8$  years)<sup>52-54,96</sup> oral contraceptive users. However, these cancers are extremely rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one

per million users. It is unknown whether ORTHO EVRA<sup>®</sup> is distinct from oral contraceptives in this regard.

## **5. Ocular Lesions**

There have been clinical case reports of retinal thrombosis associated with the use of hormonal contraceptives. ORTHO EVRA<sup>®</sup> should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

## **6. Hormonal Contraceptive Use Before or During Early Pregnancy**

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy<sup>56,57</sup>. Studies also do not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned<sup>55,56,58,59</sup>, when oral contraceptives are taken inadvertently during early pregnancy.

Combination hormonal contraceptives such as ORTHO EVRA<sup>®</sup> should not be used to induce withdrawal bleeding as a test for pregnancy. ORTHO EVRA<sup>®</sup> should not be used during pregnancy to treat threatened or habitual abortion. It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out. If the patient has not adhered to the prescribed schedule for the use of ORTHO EVRA<sup>®</sup> the possibility of pregnancy should be considered at the time of the first missed period. Hormonal contraceptive use should be discontinued if pregnancy is confirmed.

## **7. Gallbladder Disease**

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of hormonal contraceptives and estrogens<sup>60,61</sup>. More recent studies, however, have shown that the relative risk of developing gallbladder disease among hormonal contraceptive users may be minimal<sup>62-64</sup>. The recent findings of minimal risk may be related to the use of hormonal contraceptive formulations containing lower hormonal doses of estrogens and progestins.

Combination hormonal contraceptives such as ORTHO EVRA<sup>®</sup> may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women. Women with a history of combination hormonal contraceptive-related cholestasis are more likely to have the condition recur with subsequent combination hormonal contraceptive use.

## **8. Carbohydrate and Lipid Metabolic Effects**

Hormonal contraceptives have been shown to cause a decrease in glucose tolerance in some users<sup>17</sup>. However, in the non-diabetic woman, combination hormonal contraceptives appear to have no effect on fasting blood glucose<sup>67</sup>. Prediabetic and diabetic women in particular should be carefully monitored while taking combination hormonal contraceptives such as ORTHO EVRA<sup>®</sup>.

In clinical trials with oral contraceptives containing ethinyl estradiol and norgestimate there were no clinically significant changes in fasting blood glucose levels. There were no clinically significant changes in glucose levels over 24 cycles of use. Moreover, glucose tolerance tests showed no clinically significant changes from baseline to cycles 3, 12 and 24. In a 6-cycle clinical trial with ORTHO EVRA<sup>®</sup> there were no clinically significant changes in fasting blood glucose from baseline to end of treatment.

A small proportion of women will have persistent hypertriglyceridemia while taking hormonal contraceptives. As discussed earlier (see WARNINGS 1a and 1d), changes in serum triglycerides and lipoprotein levels have been reported in hormonal contraceptive users.

## **9. Elevated Blood Pressure**

Women with significant hypertension should not be started on hormonal contraception<sup>103</sup>. Women with a history of hypertension or hypertension-related diseases, or renal disease<sup>70</sup> should be encouraged to use another method of contraception. If women elect to use ORTHO EVRA<sup>®</sup>, they should be monitored closely and if a clinically significant elevation of blood pressure occurs, ORTHO EVRA<sup>®</sup> should be discontinued. For most women, elevated blood pressure will return to normal after stopping hormonal contraceptives, and there is no difference in the occurrence of hypertension between former and never users<sup>68-71</sup>.

An increase in blood pressure has been reported in women taking hormonal contraceptives<sup>68</sup> and this increase is more likely in older hormonal contraceptive users<sup>69</sup> and with extended duration of use<sup>61</sup>. Data from the Royal College of General Practitioners<sup>12</sup> and subsequent randomized trials have shown that the incidence of hypertension increases with increasing progestational activity.

## **10. Headache**

The onset or exacerbation of migraine headache or the development of headache with a new pattern that is recurrent, persistent or severe requires discontinuation of ORTHO EVRA<sup>®</sup> and evaluation of the cause.

## **11. Bleeding Irregularities**

Breakthrough bleeding and spotting are sometimes encountered in women using ORTHO EVRA<sup>®</sup>. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy, other pathology, or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another contraceptive product may resolve the bleeding. In the event of amenorrhea, pregnancy should be ruled out before initiating use of ORTHO EVRA<sup>®</sup>.

Some women may encounter amenorrhea or oligomenorrhea after discontinuation of hormonal contraceptive use, especially when such a condition was pre-existent.

### **Bleeding Patterns:**

In the clinical trials most women started their withdrawal bleeding on the fourth day of the drug-free interval, and the median duration of withdrawal bleeding was 5 to 6 days. On average 26% of women per cycle had 7 or more total days of bleeding and/or spotting (this includes both withdrawal flow and breakthrough bleeding and/or spotting).

## **12. Ectopic Pregnancy**

Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

## **PRECAUTIONS**

**Women should be counseled that ORTHO EVRA<sup>®</sup> does not protect against HIV infection (AIDS) and other sexually transmitted infections.**

### **1. Body Weight $\geq$ 198 lbs. (90 kg)**

Results of clinical trials suggest that ORTHO EVRA<sup>®</sup> may be less effective in women with body weight  $\geq$ 198 lbs. (90 kg) than in women with lower body weights.

### **2. Physical Examination and Follow-Up**

It is good medical practice for women using ORTHO EVRA<sup>®</sup>, as for all women, to have annual medical evaluation and physical examinations. The physical examination, however, may be deferred until after initiation of hormonal contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy or other pathology. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

### **3. Lipid Disorders**

Women who are being treated for hyperlipidemias should be followed closely if they elect to use ORTHO EVRA<sup>®</sup>. Some progestins may elevate LDL levels and may render the control of hyperlipidemias more difficult.

### **4. Liver Function**

If jaundice develops in any woman using ORTHO EVRA<sup>®</sup>, the medication should be discontinued. The hormones in ORTHO EVRA<sup>®</sup> may be poorly metabolized in patients with impaired liver function.

### **5. Fluid Retention**

Steroid hormones like those in ORTHO EVRA<sup>®</sup> may cause some degree of fluid retention. ORTHO EVRA<sup>®</sup> should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

### **6. Emotional Disorders**

Women who become significantly depressed while using combination hormonal contraceptives such as ORTHO EVRA<sup>®</sup> should stop the medication and use another method of contraception in an attempt to determine whether the symptom is drug related. Women with a history of depression should be carefully observed and ORTHO EVRA<sup>®</sup> discontinued if significant depression occurs.

### **7. Contact Lenses**

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

### **8. Drug Interactions**

#### **Changes in Contraceptive Effectiveness Associated With Co-Administration of Other Drugs:**

Contraceptive effectiveness may be reduced when hormonal contraceptives are co-administered with some antibiotics, antifungals, anticonvulsants, and other drugs that increase metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include barbiturates, griseofulvin, rifampin, phenylbutazone, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate and possibly with ampicillin.

The proposed mechanism of interaction of antibiotics is different from that of liver enzyme-inducing drugs. Literature suggests possible interactions with the concomitant use of hormonal contraceptives and ampicillin or tetracycline. In a pharmacokinetic drug interaction study, oral administration of tetracycline HCl,

500 mg q.i.d. for 3 days prior to and 7 days during wear of ORTHO EVRA<sup>®</sup> did not significantly affect the pharmacokinetics of norelgestromin or EE.

Several of the anti-HIV protease inhibitors have been studied with co-administration of oral combination hormonal contraceptives; significant changes (increase and decrease) in the mean AUC of the estrogen and progestin have been noted in some cases. The efficacy and safety of oral contraceptive products may be affected; it is unknown whether this applies to ORTHO EVRA<sup>®</sup>. Healthcare professionals should refer to the label of the individual anti-HIV protease inhibitors for further drug-drug interaction information.

Herbal products containing St. John's Wort (*hypericum perforatum*) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

**Increase in Plasma Hormone Levels Associated With Co-Administered Drugs:** Co-administration of atorvastatin and certain oral contraceptives containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP 3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

**Changes in Plasma Levels of Co-Administered Drugs:**

Combination hormonal contraceptives containing some synthetic estrogens (e.g., ethinyl estradiol) may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of oral contraceptives. In addition, oral contraceptives may induce the conjugation of other compounds. Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine and clofibric acid have been noted when these drugs were administered with oral contraceptives.

Although norelgestromin and its metabolites inhibit a variety of P450 enzymes in human liver microsomes, the clinical consequence of such an interaction on the levels of other concomitant medications is likely to be insignificant. Under the recommended dosing regimen, the *in vivo* concentrations of norelgestromin and its metabolites, even at the peak serum levels, are relatively low compared to the inhibitory constant ( $K_i$ ) (based on results of *in vitro* studies).

Health care professionals are advised to also refer to prescribing information of co-administered drugs for recommendations regarding management of concomitant therapy.

## **9. Interactions With Laboratory Tests**

Certain endocrine and liver function tests and blood components may be affected by hormonal contraceptives:

- a. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
- b. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.
- c. Other binding proteins may be elevated in serum.
- d. Sex hormone binding globulins are increased and result in elevated levels of total circulating endogenous sex steroids and corticoids; however, free or biologically active levels either decrease or remain unchanged.
- e. Triglycerides may be increased and levels of various other lipids and lipoproteins may be affected.
- f. Glucose tolerance may be decreased.
- g. Serum folate levels may be depressed by hormonal contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing ORTHO EVRA<sup>®</sup>.

## **10. Carcinogenesis**

No carcinogenicity studies were conducted with norelgestromin. However, bridging PK studies were conducted using doses of norgestimate (NGM)/EE which were used previously in the 2-year rat carcinogenicity study and 10-year monkey toxicity study to support the approval of ORTHO-CYCLEN<sup>®</sup> and ORTHO TRI-CYCLEN<sup>®</sup> under NDAs 19-653 and 19-697, respectively. The PK studies demonstrated that rats and monkeys were exposed to 16 and 8 times the human exposure, respectively, with the proposed ORTHO EVRA<sup>®</sup> transdermal contraceptive system.

Norelgestromin was tested in in-vitro mutagenicity assays (bacterial plate incorporation mutation assay, CHO/HGPRT mutation assay, chromosomal aberration assay using cultured human peripheral lymphocytes) and in one in-vivo test (rat micronucleus assay) and found to have no genotoxic potential.

See WARNINGS Section.

## **11. Pregnancy**

Pregnancy Category X. See CONTRAINDICATIONS and WARNINGS Sections.

Norelgestromin was tested for its reproductive toxicity in a rabbit developmental toxicity study by the SC route of administration. Doses of 0, 1, 2, 4 and 6 mg/kg body weight, which gave systemic exposure of approximately 25 to 125 times the human exposure with ORTHO EVRA<sup>®</sup>, were administered daily on gestation days 7–19. Malformations reported were paw hyperflexion at 4 and 6 mg/kg and paw hyperextension and cleft palate at 6 mg/kg.

## **12. Nursing Mothers**

The effects of ORTHO EVRA<sup>®</sup> in nursing mothers have not been evaluated and are unknown. Small amounts of combination hormonal contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, combination hormonal contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. Long-term follow-up of infants whose mothers used combination hormonal contraceptives while breast feeding has shown no deleterious effects. However, the nursing mother should be advised not to use ORTHO EVRA<sup>®</sup> but to use other forms of contraception until she has completely weaned her child.

## **13. Pediatric Use**

Safety and efficacy of ORTHO EVRA<sup>®</sup> have been established in women of reproductive age. Safety and efficacy are expected to be the same for post-pubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

## **14. Geriatric Use**

This product has not been studied in women over 65 years of age and is not indicated in this population.

## **15. Sexually Transmitted Diseases**

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

## **16. Patch Adhesion**

Experience with more than 70,000 ORTHO EVRA<sup>®</sup> patches worn for contraception for 6-13 cycles showed that 4.7% of patches were replaced because they either fell off (1.8%) or were partly detached (2.9%). Similarly, in a small study of patch wear

under conditions of physical exertion and variable temperature and humidity, less than 2% of patches were replaced for complete or partial detachment.

If the ORTHO EVRA<sup>®</sup> patch becomes partially or completely detached and remains detached, insufficient drug delivery occurs. A patch should not be re-applied if it is no longer sticky, if it has become stuck to itself or another surface, if it has other material stuck to it, or if it has become loose or fallen off before. If a patch cannot be re-applied, a new patch should be applied immediately. Supplemental adhesives or wraps should not be used to hold the ORTHO EVRA<sup>®</sup> patch in place.

If a patch is partially or completely detached for more than one day (24 hours or more) OR if the woman is not sure how long the patch has been detached, she may not be protected from pregnancy. She should stop the current contraceptive cycle and start a new cycle immediately by applying a new patch. Back-up contraception, such as condoms, spermicide, or diaphragm, must be used for the first week of the new cycle.

## **INFORMATION FOR THE PATIENT**

See Patient Labeling printed below.

### **ADVERSE REACTIONS**

The most common adverse events reported by 9 to 22% of women using ORTHO EVRA<sup>®</sup> in clinical trials (N= 3,330) were the following, in order of decreasing incidence: breast symptoms, headache, application site reaction, nausea, upper respiratory infection, menstrual cramps, and abdominal pain.

The most frequent adverse events leading to discontinuation in 1 to 2.4% of women using ORTHO EVRA<sup>®</sup> in the trials included the following: nausea and/or vomiting, application site reaction, breast symptoms, headache, and emotional lability.

Listed below are adverse events that have been associated with the use of combination hormonal contraceptives. These are also likely to apply to combination transdermal hormonal contraceptives such as ORTHO EVRA<sup>®</sup>.

An increased risk of the following serious adverse reactions has been associated with the use of combination hormonal contraceptives (see WARNINGS Section).

- Thrombophlebitis and venous thrombosis with or without embolism
- Arterial thromboembolism
- Pulmonary embolism
- Myocardial infarction

- Cerebral hemorrhage
- Cerebral thrombosis
- Hypertension
- Gallbladder disease
- Hepatic adenomas or benign liver tumors

There is evidence of an association between the following conditions and the use of combination hormonal contraceptives:

- Mesenteric thrombosis
- Retinal thrombosis

The following adverse reactions have been reported in users of combination hormonal contraceptives and are believed to be drug-related:

- Nausea
- Vomiting
- Gastrointestinal symptoms (such as abdominal cramps and bloating)
- Breakthrough bleeding
- Spotting
- Change in menstrual flow
- Amenorrhea
- Temporary infertility after discontinuation of treatment
- Edema
- Melasma which may persist
- Breast changes: tenderness, enlargement, secretion
- Change in weight (increase or decrease)
- Change in cervical erosion and secretion
- Diminution in lactation when given immediately postpartum
- Cholestatic jaundice
- Migraine
- Rash (allergic)
- Mental depression
- Reduced tolerance to carbohydrates
- Vaginal candidiasis
- Change in corneal curvature (steepening)

- Intolerance to contact lenses

The following adverse reactions have been reported in users of combination hormonal contraceptives and a cause and effect association has been neither confirmed nor refuted:

- Pre-menstrual syndrome
- Cataracts
- Changes in appetite
- Cystitis-like syndrome
- Headache
- Nervousness
- Dizziness
- Hirsutism
- Loss of scalp hair
- Erythema multiforme
- Erythema nodosum
- Hemorrhagic eruption
- Vaginitis
- Porphyria
- Impaired renal function
- Hemolytic uremic syndrome
- Acne
- Changes in libido
- Colitis
- Budd-Chiari Syndrome

#### **OVERDOSAGE**

Serious ill effects have not been reported following accidental ingestion of large doses of hormonal contraceptives. Overdosage may cause nausea and vomiting, and withdrawal bleeding may occur in females. Given the nature and design of the ORTHO EVRA<sup>®</sup> patch, it is unlikely that overdosage will occur. Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. In case of suspected overdose, all ORTHO EVRA<sup>®</sup> patches should be removed and symptomatic treatment given.

## DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, ORTHO EVRA<sup>®</sup> must be used exactly as directed.

Complete instructions to facilitate patient counseling on proper system usage may be found in the Detailed Patient Labeling.

### Transdermal Contraceptive System Overview

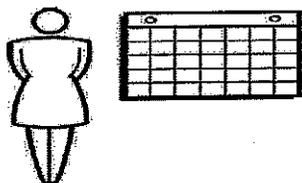
ORTHO EVRA<sup>®</sup> is a combination transdermal contraceptive that contains 6.00 mg norelgestromin (NGMN) and 0.75mg ethinyl estradiol (EE). Systemic exposures (as measured by AUC and C<sub>ss</sub>) of NGMN and EE during use of ORTHO EVRA<sup>®</sup> are higher and peak concentrations (C<sub>max</sub>) are lower than those produced by an oral contraceptive containing norgestimate 250 µg / EE 35 µg. (See **BOLDED WARNING; CLINICAL PHARMACOLOGY, Transdermal versus Oral Contraceptives**).

This system uses a 28-day (four-week) cycle. A new patch is applied each week for three weeks (21 total days). Week Four is patch-free. Withdrawal bleeding is expected during this time.

Every new patch should be applied on the same day of the week. This day is known as the "Patch Change Day." For example, if the first patch is applied on a Monday, all subsequent patches should be applied on a Monday. Only one patch should be worn at a time.

The ORTHO EVRA<sup>®</sup> patch should not be cut, damaged or altered in any way. If the ORTHO EVRA<sup>®</sup> patch is cut, damaged or altered in size, contraceptive efficacy may be impaired.

On the day after Week Four ends a new four-week cycle is started by applying a new patch. Under no circumstances should there be more than a seven-day patch-free interval between dosing cycles.



If the woman is starting ORTHO EVRA<sup>®</sup> for the first time, she should wait until the day she begins her menstrual period. Either a First Day start or Sunday start may be chosen (see below). The day she applies her first patch will be Day 1. Her "Patch Change Day" will be on this day every week.

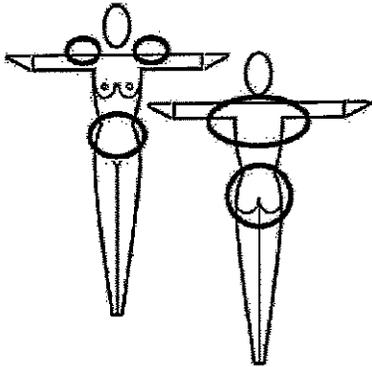
**CHOOSE ONE OPTION:**



**First Day Start**

OR

**Sunday Start**



- for **First Day Start**: the patient should apply her first patch during the first 24 hours of her menstrual period.

If therapy starts after Day 1 of the menstrual cycle, a non-hormonal back-up contraceptive (such as a condoms, spermicide, or diaphragm) should be used concurrently for the first 7 consecutive days of the first treatment cycle.

- for **Sunday Start**: the woman should apply her first patch on the first Sunday after her menstrual period starts. She must use back-up contraception for the first week of her first cycle.

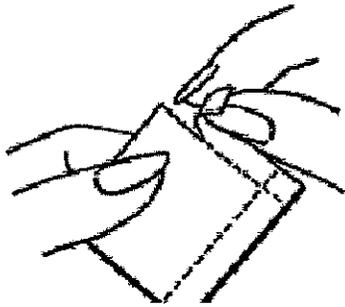
If the menstrual period begins on a Sunday, the first patch should be applied on that day, and no back-up contraception is needed.

**Where to apply the patch.** The patch should be applied to clean, dry, intact healthy skin on the buttock, abdomen, upper outer arm or upper torso, in a place where it won't be rubbed by tight clothing. ORTHO EVRA<sup>®</sup> should not be placed on skin that is red, irritated or cut, nor should it be placed on the breasts.

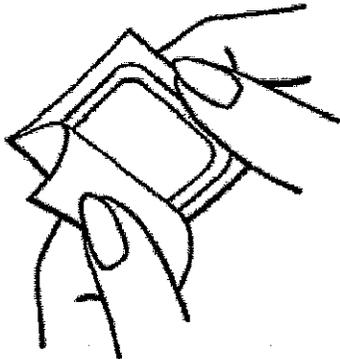
To prevent interference with the adhesive properties of ORTHO EVRA<sup>®</sup>, no make-up, creams, lotions, powders or other topical products should be applied to the skin area where the ORTHO EVRA<sup>®</sup> patch is or will be placed.

### Application of the ORTHO EVRA® patch

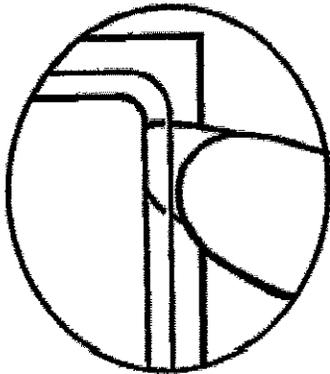
The foil pouch is opened by tearing it along the edge using the fingers.



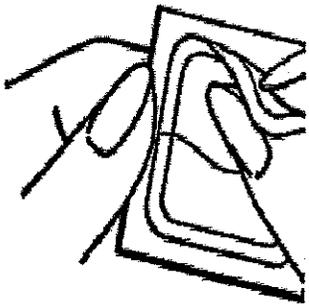
The foil pouch should be peeled apart and open flat



A corner of the patch is grasped firmly and it is gently removed from the foil pouch.



The woman should be instructed to use her fingernail, to lift one corner of the patch and peel the patch and the plastic liner off the foil liner. Sometimes patches can stick to the inside of the pouch – the woman should be careful not to accidentally remove the clear liner as she removes the patch.

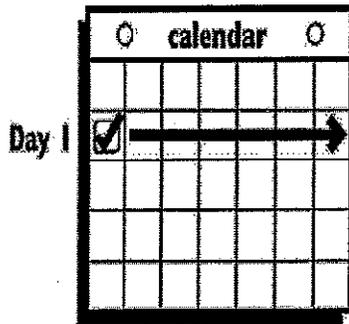




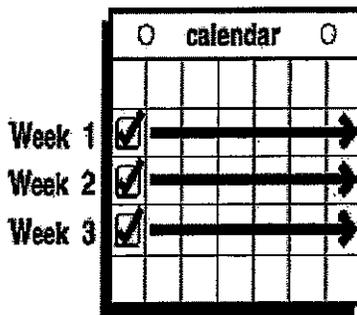
Half of the clear protective liner is to be peeled away. (The woman should avoid touching the sticky surface of the patch).



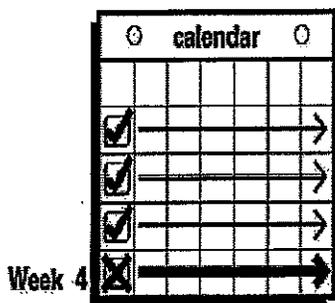
The sticky surface of the patch is applied to the skin and the other half of the liner is removed. The woman should press down firmly on the patch with the palm of her hand for 10 seconds, making sure that the edges stick well. She should check her patch every day to make sure it is sticking.



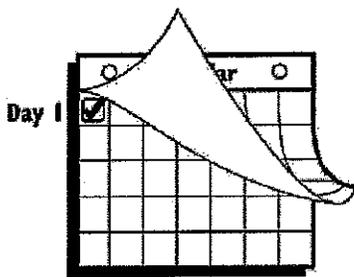
The patch is worn for seven days (one week). On the “Patch Change Day”, Day 8, the used patch is removed and a new one is applied immediately. The used patch still contains some active hormones – it should be carefully folded in half so that it sticks to itself before safely disposing of it in the trash. Used patches should not be flushed down the toilet.



A new patch is applied for Week Two (on Day 8) and again for Week Three (on Day 15), on the usual “Patch Change Day”. Patch changes may occur at any time on the Change Day. Each new ORTHO EVRA<sup>®</sup> patch should be applied to a new spot on the skin to help avoid irritation, although they may be kept within the same anatomic area.



Week Four is patch-free (Day 22 through Day 28), thus completing the four-week contraceptive cycle. Bleeding is expected to begin during this time.



The next four-week cycle is started by applying a new patch on the usual "Patch Change Day," the day after Day 28, no matter when the menstrual period begins or ends.

Under no circumstances should there be more than a seven-day patch-free interval between patch cycles.

If the ORTHO EVRA<sup>®</sup> patch becomes partially or completely detached and remains detached, insufficient drug delivery occurs.

***If a patch is partially or completely detached:***

- for less than one day (up to 24 hours), the woman should try to reapply it to the same place or replace it with a new patch immediately. No back-up contraception is needed. The woman's "Patch Change Day" will remain the same.
- for more than one day (24 hours or more) OR if the woman is not sure how long the patch has been detached, SHE MAY NOT BE PROTECTED FROM PREGNANCY. She should stop the current contraceptive cycle and start a new cycle immediately by applying a new patch. There is now a new "Day 1" and a new "Patch Change Day." Back-up contraception, such as condoms, spermicide, or diaphragm, must be used for the first week of the new cycle.

A patch should not be re-applied if it is no longer sticky, if it has become stuck to itself or another surface, if it has other material stuck to it or if it has previously become loose or fallen off. If a patch cannot be re-applied, a new patch should be applied immediately. Supplemental adhesives or wraps should not be used to hold the ORTHO EVRA<sup>®</sup> patch in place.

**If the woman forgets to change her patch**

- at the start of any patch cycle (Week One /Day 1): SHE MAY NOT BE PROTECTED FROM PREGNANCY. She should apply the first patch of her new cycle as soon as she remembers. There is now a new "Patch Change Day"

and a new “Day 1.” The woman must use back-up contraception, such as condoms, spermicide, or diaphragm, for the first week of the new cycle.

- **in the middle of the patch cycle (Week Two/Day 8 or Week Three/Day 15),**
  - for **one or two days** (up to 48 hours), she should apply a new patch immediately. The next patch should be applied on the usual “Patch Change Day.” No back-up contraception is needed.
  - for **more than two days** (48 hours or more), SHE MAY NOT BE PROTECTED FROM PREGNANCY. She should stop the current contraceptive cycle and start a new four-week cycle immediately by putting on a new patch. There is now a new “Patch Change Day” and a new “Day 1.” The woman must use back-up contraception for one week.
- **at the end of the patch cycle (Week Four/Day 22),**

Week Four (Day 22): If the woman forgets to remove her patch, she should take it off as soon as she remembers. The next cycle should be started on the usual “Patch Change Day,” which is the day after Day 28. No back-up contraception is needed.

**Under no circumstances should there be more than a seven-day patch-free interval between cycles.** If there are more than seven patch-free days, THE WOMAN MAY NOT BE PROTECTED FROM PREGNANCY and back-up contraception, such as condoms, spermicide, or diaphragm, must be used for seven days. As with combined oral contraceptives, the risk of ovulation increases with each day beyond the recommended drug-free period. If coital exposure has occurred during such an extended patch-free interval, the possibility of fertilization should be considered.

### **Change Day Adjustment**

If the woman wishes to change her Patch Change Day she should complete her current cycle, removing the third ORTHO EVRA<sup>®</sup> patch on the correct day. During the patch-free week, she may select an earlier Patch Day Change by applying a new ORTHO EVRA<sup>®</sup> patch on the desired day. In no case should there be more than 7 consecutive patch-free days.

### **Switching From an Oral Contraceptive**

Treatment with ORTHO EVRA<sup>®</sup> should begin on the first day of withdrawal bleeding. If there is no withdrawal bleeding within 5 days of the last active (hormone-containing) tablet, pregnancy must be ruled out. If therapy starts later than the first day of withdrawal bleeding, a non-hormonal contraceptive should be used concurrently for 7 days. If more than 7 days elapse after taking the last active oral contraceptive tablet, the possibility of ovulation and conception should be considered.

### **Use After Childbirth**

Women who elect not to breast-feed should start contraceptive therapy with ORTHO EVRA<sup>®</sup> no sooner than 4 weeks after childbirth. If a woman begins using ORTHO EVRA<sup>®</sup> postpartum, and has not yet had a period, the possibility of ovulation and conception occurring prior to use of ORTHO EVRA<sup>®</sup> should be considered, and she should be instructed to use an additional method of contraception, such as condoms, spermicide, or diaphragm, for the first seven days. (See Precautions: Nursing Mothers, and Warnings: Thromboembolic and Other Vascular Problems.)

### **Use After Abortion or Miscarriage<sup>106</sup>**

After an abortion or miscarriage that occurs in the first trimester, ORTHO EVRA<sup>®</sup> may be started immediately. An additional method of contraception is not needed if ORTHO EVRA<sup>®</sup> is started immediately. If use of ORTHO EVRA<sup>®</sup> is not started within 5 days following a first trimester abortion, the woman should follow the instructions for a woman starting ORTHO EVRA<sup>®</sup> for the first time. In the meantime she should be advised to use a non-hormonal contraceptive method. Ovulation may occur within 10 days of an abortion or miscarriage.

ORTHO EVRA<sup>®</sup> should be started no earlier than 4 weeks after a second trimester abortion or miscarriage. When ORTHO EVRA<sup>®</sup> is used postpartum or postabortion, the increased risk of thromboembolic disease must be considered. (See CONTRAINDICATIONS and WARNINGS concerning thromboembolic disease. See PRECAUTIONS for “Nursing Mothers”.)

### **Breakthrough Bleeding or Spotting**

In the event of breakthrough bleeding or spotting (bleeding that occurs on the days that ORTHO EVRA<sup>®</sup> is worn), treatment should be continued. If breakthrough bleeding persists longer than a few cycles, a cause other than ORTHO EVRA<sup>®</sup> should be considered.

In the event of no withdrawal bleeding (bleeding that should occur during the patch-free week), treatment should be resumed on the next scheduled Change Day. If ORTHO EVRA<sup>®</sup> has been used correctly, the absence of withdrawal bleeding is not necessarily an indication of pregnancy. Nevertheless, the possibility of pregnancy should be considered, especially if absence of withdrawal bleeding occurs in 2 consecutive cycles. ORTHO EVRA<sup>®</sup> should be discontinued if pregnancy is confirmed.

### **In Case of Vomiting or Diarrhea**

Given the nature of transdermal application, dose delivery should be unaffected by vomiting.

### **In Case of Skin Irritation**

If patch use results in uncomfortable irritation, the patch may be removed and a new patch may be applied to a different location until the next Change Day. Only one patch should be worn at a time.

### **ADDITIONAL INSTRUCTIONS FOR DOSING**

Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing hormonal contraceptives. In case of breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be considered. In case of undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another method of contraception may solve the problem.

### **Use of Hormonal Contraceptives in the Event of a Missed Menstrual Period:**

1. If the woman has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Hormonal contraceptive use should be discontinued if pregnancy is confirmed.
2. If the woman has adhered to the prescribed regimen and misses one period, she should continue using her contraceptive patches.
3. If the woman has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out. ORTHO EVRA<sup>®</sup> use should be discontinued if pregnancy is confirmed.

### **HOW SUPPLIED**

Each beige ORTHO EVRA<sup>®</sup> patch contains 6.00mg norelgestromin and 0.75 mg EE.

Each patch surface is heat stamped with ORTHO EVRA<sup>®</sup>. Each patch is packaged in a protective pouch.

ORTHO EVRA<sup>®</sup> is available in folding cartons of 1 cycle each (NDC # 0062-1920-15); each cycle contains 3 patches.

ORTHO EVRA<sup>®</sup> is also available in folding cartons containing a single patch (NDC # 0062-1920-01), intended for use as a replacement in the event that a patch is inadvertently lost or destroyed.

### **Special Precautions for Storage and Disposal**

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Store patches in their protective pouches. Apply immediately upon removal from the protective pouch.

Do not store in the refrigerator or freezer.

Used patches still contain some active hormones. Each patch should be carefully folded in half so that it sticks to itself before safely disposing of it in the trash. Used patches should not be flushed down the toilet.

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## **DETAILED PATIENT LABELING**

### **ORTHO EVRA® (norelgestromin/ethinyl estradiol transdermal system)**

**Rx only**

**This product is intended to prevent pregnancy. It does not protect against HIV (AIDS) or other sexually transmitted diseases.**

## **DESCRIPTION**

The contraceptive patch ORTHO EVRA® is a thin, beige, plastic patch that sticks to the skin. The sticky part of the patch contains the following hormones: norelgestromin (progestin) and ethinyl estradiol (estrogen). These hormones are absorbed continuously through the skin and into the bloodstream. On average, the amount of estrogen delivered through the skin produces estrogen exposure that is higher than the exposure when taking a birth control pill containing 35 micrograms of estrogen. Each patch is sealed in a pouch that protects it until you are ready to wear it.

## **INTRODUCTION**

Any woman who considers using the contraceptive patch ORTHO EVRA® should understand the benefits and risks of using this form of birth control. This leaflet will give you much of the information you will need to make this decision and will also help you determine if you are at risk of developing any serious side effects. It will tell you how to use the contraceptive patch properly so that it will be as effective as possible. However, this leaflet is not a replacement for a careful discussion between you and your health care professional. You should discuss the information provided in this leaflet with him or her, both when you first start using the contraceptive patch ORTHO EVRA® and during your revisits. You should also follow your health care professional's advice with regard to regular check-ups while you are using the contraceptive patch.

## **EFFECTIVENESS OF HORMONAL CONTRACEPTIVE METHODS**

Hormonal contraceptives, including ORTHO EVRA<sup>®</sup>, are used to prevent pregnancy and are more effective than most other non-surgical methods of birth control. When ORTHO EVRA<sup>®</sup> is used correctly, the chance of becoming pregnant is approximately 1% (1 pregnancy per 100 women per year of use when used correctly), which is comparable to that of the pill. The chance of becoming pregnant increases with incorrect use.

Clinical trials suggested that ORTHO EVRA<sup>®</sup> may be less effective in women weighing more than 198 lbs. (90 kg). If you weigh more than 198 lbs. (90 kg) you should talk to your health care professional about which method of birth control may be best for you.

Typical failure rates for other methods of birth control during the first year of use are as follows:

Implant: <1%  
Injection: <1%  
IUD: <1-2%  
Diaphragm with spermicides: 20%  
Spermicides alone: 26%  
Female sterilization: <1%  
Male sterilization: <1%  
Cervical Cap with spermicide: 20 to 40%  
Condom alone (male): 14%  
Condom alone (female): 21%  
Periodic abstinence: 25%  
No birth control method: 85%  
Withdrawal: 19%

### **WHO SHOULD NOT USE ORTHO EVRA<sup>®</sup>**

Hormonal contraceptives include birth control pills, injectables, implants, the vaginal ring, and the contraceptive patch. The following information is derived primarily from studies of birth control pills. The contraceptive patch is expected to be associated with similar risks:

**Cigarette smoking increases the risk of serious cardiovascular side effects from hormonal contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use hormonal contraceptives, including ORTHO EVRA<sup>®</sup>, are strongly advised not to smoke.**

Some women should not use the ORTHO EVRA<sup>®</sup> contraceptive patch. For example, you should not use ORTHO EVRA<sup>®</sup> if you are pregnant or think you may be pregnant. You should also not use ORTHO EVRA<sup>®</sup> if you have any of the following conditions:

- A history of heart attack or stroke
- Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), or eyes
- A history of blood clots in the deep veins of your legs
- Chest pain (angina pectoris)
- Known or suspected breast cancer or cancer of the lining of the uterus, cervix or vagina.
- Unexplained vaginal bleeding (until your doctor reaches a diagnosis)
- Hepatitis or yellowing of the whites of your eyes or of the skin (jaundice) during pregnancy or during previous use of hormonal contraceptives such as ORTHO EVRA<sup>®</sup>, NORPLANT, or the birth control pill
- Liver tumor (benign or cancerous)
- Known or suspected pregnancy
- Severe high blood pressure
- Diabetes with complications of the kidneys, eyes, nerves, or blood vessels
- Headaches with neurological symptoms
- Use of oral contraceptives (birth control pills)
- Disease of heart valves with complications
- Need for a prolonged period of bed rest following major surgery
- An allergic reaction to any of the components of ORTHO EVRA<sup>®</sup>

Tell your health care professional if you have ever had any of these conditions. Your health care professional can recommend a non-hormonal method of birth control.

#### **OTHER CONSIDERATIONS BEFORE USING ORTHO EVRA<sup>®</sup>**

Hormones from patches applied to the skin get into the blood stream and are removed from the body differently than hormones from birth control pills taken by mouth. **You will be exposed to about 60% more estrogen if you use ORTHO EVRA<sup>®</sup> than if you use a typical birth control pill containing 35 micrograms of estrogen.** In general, increased estrogen exposure may increase the risk of side effects.

The risk of venous thromboembolic disease (blood clots in the legs and/or the lungs) may be increased with ORTHO EVRA<sup>®</sup> compared with that of oral contraceptives containing norgestimate and 35mcg of estrogen. This risk has been examined in two

separate studies. Both studies were conducted using information from insurance claims. One study, which in addition reviewed patient charts, found a doubling of the risk for thromboembolic disease in users of ORTHO EVRA<sup>®</sup> compared with women using these oral contraceptives, and another study found no increase in risk of thromboembolic disease for women using ORTHO EVRA<sup>®</sup>. You should discuss this possible increased risk with your healthcare provider before using ORTHO EVRA<sup>®</sup>. Call your healthcare professional immediately should any of the adverse effects listed under “WARNING SIGNALS” occur while you are using ORTHO EVRA<sup>®</sup>. (See below.)

Also talk to your health care professional about using ORTHO EVRA<sup>®</sup> if:

- you smoke
- you are recovering from the birth of a baby
- you are recovering from a second trimester miscarriage or abortion
- you are breast-feeding
- you weigh 198 pounds or more
- you are taking any other medications
- Also, tell your health care professional if you have or have had:
  - Breast nodules, fibrocystic disease of the breast, an abnormal breast x-ray or mammogram
  - A family history of breast cancer
  - Diabetes
  - Elevated cholesterol or triglycerides
  - High blood pressure
  - Migraine or other headaches or epilepsy
  - Depression
  - Gallbladder disease
  - Liver disease
  - Heart disease
  - Kidney disease
  - Scanty or irregular menstrual periods

If you have any of these conditions you should be checked often by your health care professional if you use the contraceptive patch.

## **RISKS OF USING HORMONAL CONTRACEPTIVES, INCLUDING ORTHO EVRA<sup>®</sup>**

The following information is derived primarily from studies of birth control pills. Since ORTHO EVRA<sup>®</sup> contains hormones similar to those found in birth control pills, it is expected to be associated with similar risks:

### **1. Risk of Developing Blood Clots**

Blood clots and blockage of blood vessels that can cause death or serious disability are some of the most serious side effects of using hormonal contraceptives, including the ORTHO EVRA<sup>®</sup> contraceptive patch. In particular, a clot in the legs can cause thrombophlebitis, and a clot that travels to the lungs can cause sudden blocking of the vessel carrying blood to the lungs. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.

The risk of venous thromboembolic disease (blood clots in the legs and/or the lungs) may be increased with ORTHO EVRA<sup>®</sup> compared with that of oral contraceptives containing norgestimate and 35mcg of estrogen (see the earlier Section OTHER CONSIDERATIONS BEFORE USING ORTHO EVRA<sup>®</sup>). You should discuss this possible increased risk with your healthcare professional before using ORTHO EVRA<sup>®</sup>. Call your healthcare professional immediately should any of the adverse effects listed under "WARNING SIGNALS" occur while you are using ORTHO EVRA<sup>®</sup>. (See below.)

If you use ORTHO EVRA<sup>®</sup> and need elective surgery, need to stay in bed for a prolonged illness or injury or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your doctor about stopping ORTHO EVRA<sup>®</sup> four weeks before surgery and not using it for two weeks after surgery or during bed rest. You should also not use ORTHO EVRA<sup>®</sup> soon after delivery of a baby. It is advisable to wait for at least four weeks after delivery if you are not breast-feeding. If you are breast-feeding, you should wait until you have weaned your child before using ORTHO EVRA<sup>®</sup>. (See also the section on Breast-Feeding in General Precautions.)

### **2. Heart Attacks and Strokes**

Hormonal contraceptives, including ORTHO EVRA<sup>®</sup>, may increase the risk of developing strokes (blockage or rupture of blood vessels in the brain) and angina pectoris and heart attacks (blockage of blood vessels in the heart). Any of these conditions can cause death or serious disability.

Smoking and the use of hormonal contraceptives including ORTHO EVRA<sup>®</sup> greatly increase the chances of developing and dying of heart disease. Smoking also greatly increases the possibility of suffering heart attacks and strokes.

### **3. Gallbladder Disease**

Women who use hormonal contraceptives, including ORTHO EVRA<sup>®</sup>, probably have a greater risk than nonusers of having gallbladder disease.

### **4. Liver Tumors**

In rare cases, combination oral contraceptives can cause benign but dangerous liver tumors. Since ORTHO EVRA<sup>®</sup> contains hormones similar to those in birth control pills, this association may also exist with ORTHO EVRA<sup>®</sup>. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, some studies report an increased risk of developing liver cancer. However, liver cancers are rare.

### **5. Cancer of the Reproductive Organs and Breasts**

Various studies give conflicting reports on the relationship between breast cancer and hormonal contraceptive use. Combination hormonal contraceptives, including ORTHO EVRA<sup>®</sup>, may slightly increase your chance of having breast cancer diagnosed, particularly after using hormonal contraceptives at a younger age. After you stop using hormonal contraceptives, the chances of having breast cancer diagnosed begin to go back down. You should have regular breast examinations by a health care professional and examine your own breasts monthly. Tell your health care professional if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram.

Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is usually a hormone-sensitive tumor.

Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives, although this finding may be related to factors other than the use of oral contraceptives. However, there is insufficient evidence to rule out the possibility that oral contraceptives may cause such cancers.

### **ESTIMATED RISK OF DEATH FROM A BIRTH CONTROL METHOD OR PREGNANCY**

All methods of birth control and pregnancy are associated with a risk of developing certain diseases that may lead to disability or death. An estimate of the number of deaths associated with different methods of birth control and pregnancy has been calculated and is shown in the following table.

ORTHO EVRA<sup>®</sup> is expected to be associated with similar risks as oral contraceptives:

Annual Number of Birth-Related or Method-Related Deaths Associated With Control of Fertility Per 100,000 Nonsterile Women by Fertility Control Method According to Age

Method of control and outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm / spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

\*Deaths are birth-related

\*\*Deaths are method-related

Adapted from H.W. Ory, ref. #35.

In the above table, the risk of death from any birth control method is less than the risk of childbirth, except for oral contraceptive users over the age of 35 who smoke and pill users over the age of 40 even if they do not smoke. It can be seen in the table that for women aged 15 to 39, the risk of death was highest with pregnancy (7-26 deaths per 100,000 women, depending on age). Among pill users who do not smoke, the risk of death is always lower than that associated with pregnancy for any age group, although over the age of 40, the risk increases to 32 deaths per 100,000 women, compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35, the estimated number of deaths exceeds those for other methods of birth control. If a woman is over the age of 40 and smokes, her estimated risk of death is four times higher (117/100,000 women) than the estimated risk associated with pregnancy (28/100,000 women) in that age group.

In 1989 an Advisory Committee of the FDA concluded that the benefits of low-dose hormonal contraceptive use by healthy, non-smoking women over 40 years of age may outweigh the possible risks.

### WARNING SIGNALS

If any of these adverse effects occur while you are using ORTHO EVRA<sup>®</sup>, call your doctor immediately:

- Sharp chest pain, coughing of blood, or sudden shortness of breath (indicating a possible clot in the lung)

- Pain in the calf (indicating a possible clot in the leg)
- Crushing chest pain or tightness in the chest (indicating a possible heart attack)
- Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness, or numbness in an arm or leg (indicating a possible stroke)
- Sudden partial or complete loss of vision (indicating a possible clot in the eye)
- Breast lumps (indicating possible breast cancer or fibrocystic disease of the breast; ask your doctor or health care professional to show you how to examine your breasts)
- Severe pain or tenderness in the stomach area (indicating a possibly ruptured liver tumor)
- Severe problems with sleeping, weakness, lack of energy, fatigue, or change in mood (possibly indicating severe depression)
- Jaundice or a yellowing of the skin or eyeballs accompanied frequently by fever, fatigue, loss of appetite, dark colored urine, or light colored bowel movements (indicating possible liver problems)

## **SIDE EFFECTS OF ORTHO EVRA®**

### **1. Skin Irritation**

Skin irritation, redness or rash may occur at the site of application. If this occurs, the patch may be removed and a new patch may be applied to a new location until the next Change Day. Single replacement patches are available from pharmacies.

### **2. Vaginal Bleeding**

Irregular vaginal bleeding or spotting may occur while you are using ORTHO EVRA®. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Irregular bleeding may occur during the first few months of contraceptive patch use but may also occur after you have been using the contraceptive patch for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue using your contraceptive patches on schedule. If the bleeding occurs in more than a few cycles or lasts for more than a few days, talk to your health care professional.

### **3. Problems Wearing Contact Lenses**

If you wear contact lenses and notice a change in vision or an inability to wear your lenses, contact your health care professional.

### **4. Fluid Retention or Raised Blood Pressure**

Hormonal contraceptives, including the contraceptive patch, may cause edema (fluid retention) with swelling of the fingers or ankles and may raise your blood pressure. If you experience fluid retention, contact your health care professional.

## **5. Melasma**

A spotty darkening of the skin is possible, particularly of the face. This may persist after use of hormonal contraceptives is discontinued.

## **6. Other Side Effects**

The most common side effects of ORTHO EVRA<sup>®</sup> include nausea and vomiting, breast symptoms, headache, menstrual cramps, and abdominal pain. In addition, change in appetite, nervousness, depression, dizziness, loss of scalp hair, rash, and vaginal infections may occur.

## **GENERAL PRECAUTIONS**

### **1. Weight $\geq$ 198 lbs. (90 kg)**

Clinical trials suggest that ORTHO EVRA<sup>®</sup> may be less effective in women weighing 198 lbs. (90 kg) or more compared with its effectiveness in women with lower body weights. If you weigh 198 lbs. (90 kg) or more you should talk to your health care professional about which method of birth control may be best for you.

### **2. Missed Periods and Use of ORTHO EVRA<sup>®</sup> Before or During Early Pregnancy**

There may be times when you may not menstruate regularly during your patch-free week. If you have used ORTHO EVRA<sup>®</sup> correctly and miss one menstrual period, continue using your contraceptive patches for the next cycle but be sure to inform your health care professional before doing so. If you have not used ORTHO EVRA<sup>®</sup> as instructed and missed a menstrual period, or if you missed two menstrual periods in a row, you could be pregnant. Check with your health care professional immediately to determine whether you are pregnant. Stop using ORTHO EVRA<sup>®</sup> if you are pregnant.

There is no conclusive evidence that hormonal contraceptive use causes birth defects when taken accidentally during early pregnancy. Previously, a few studies had reported that oral contraceptives might be associated with birth defects, but these findings have not been seen in more recent studies. Nevertheless, hormonal contraceptives, including ORTHO EVRA<sup>®</sup>, should not be used during pregnancy. You should check with your health care professional about risks to your unborn child from any medication taken during pregnancy.

### **3. While Breast-Feeding**

If you are breast-feeding, consult your health care professional before starting ORTHO EVRA<sup>®</sup>. Hormonal contraceptives are passed on to the child in the milk. A few adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. In addition, combination hormonal contraceptives

may decrease the amount and quality of your milk. If possible, do not use combination hormonal contraceptives such as ORTHO EVRA<sup>®</sup> while breast-feeding. You should use a barrier method of contraception since breast-feeding provides only partial protection from becoming pregnant and this partial protection decreases significantly as you breast-feed for longer periods of time. You should consider starting ORTHO EVRA<sup>®</sup> only after you have weaned your child completely.

#### **4. Laboratory Tests**

If you are scheduled for any laboratory tests, tell your doctor you are using ORTHO EVRA<sup>®</sup> since certain blood tests may be affected by hormonal contraceptives.

#### **5. Drug Interactions**

Certain drugs may interact with hormonal contraceptives, including ORTHO EVRA<sup>®</sup>, to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Such drugs include rifampin, drugs used for epilepsy such as barbiturates (for example, phenobarbital), anticonvulsants such as topiramate (TOPAMAX), carbamazepine (Tegretol is one brand of this drug), phenytoin (Dilantin is one brand of this drug), phenylbutazone (Butazolidin is one brand), certain drugs used in the treatment of HIV or AIDS, and possibly certain antibiotics. Tetracycline has been shown not to interact with ORTHO EVRA<sup>®</sup>. Pregnancies and breakthrough bleeding have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort.

As with all prescription products, you should notify your health care professional of any other medications you are taking. You may need to use a barrier contraceptive when you take drugs that can make ORTHO EVRA<sup>®</sup> less effective.

#### **6. Sexually Transmitted Diseases**

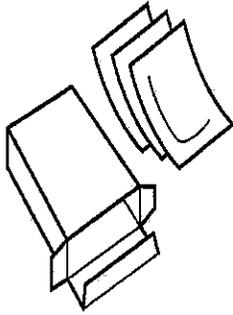
**ORTHO EVRA<sup>®</sup> is intended to prevent pregnancy. It does not protect against HIV (AIDS) or other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.**

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## HOW TO USE ORTHO EVRA®

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### Instructions for Use



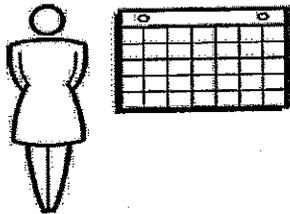
ORTHO EVRA® keeps you from becoming pregnant by transferring hormones to your body through your skin. The patch must stick securely to your skin in order for it to work properly.

This method uses a 28 day (four week) cycle. You should apply a new patch each week for three weeks (21 total days). You should not apply a patch during the fourth week. Your menstrual period should start during this patch-free week.

Every new patch should be applied on the same day of the week. This day will be your 'Patch Change Day.' *For example, if you apply your first patch on a Monday, all of your patches should be applied on a Monday.* You should wear only one patch at a time.

On the day after week four ends, you should begin a new four week cycle by applying a new patch.

**Save these instructions.**



### 1

If this is the **first time** you are using ORTHO EVRA®, **wait until the day you get your menstrual period.** *The day you apply your first patch will be Day 1. Your 'Patch Change Day' will be on this day every week.*

2

You may choose a first day start or Sunday start

CHOOSE ONE OPTION:



**First Day Start**

OR

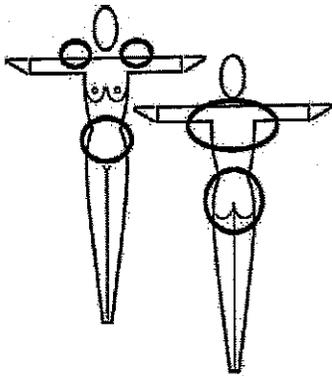
**Sunday Start**

OR

- *for First Day start:* apply your first patch during the first 24 hours of your menstrual period
- *for Sunday start:* apply your first patch on the first Sunday after your menstrual period starts. You must use back-up contraception, such as a condom, spermicide, or diaphragm for the first week of your first cycle
- The day you apply your first patch will be Day 1. Your 'Patch Change Day' will be on this day every week.

3

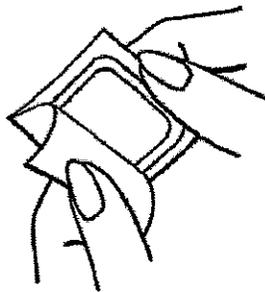
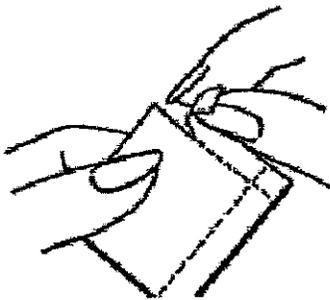
**Choose a place on your body to put the patch.** Put the patch on your buttock, abdomen, upper outer arm or upper torso, in a place where it won't be rubbed by tight clothing. *Never put the patch on your breasts. To avoid irritation, apply each new patch to a different place on your skin.*

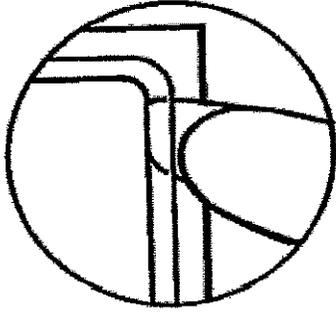


4

Open the foil pouch by tearing it along the top edge **and** one side edge.

Peel the foil pouch apart and open it flat.

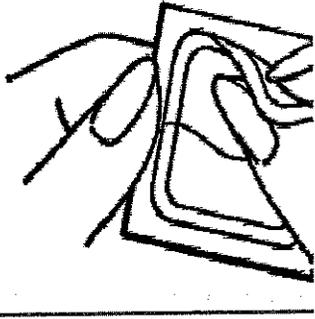




5

You will see that the patch is covered by a layer of clear plastic. It is important to remove the patch **and** the plastic together from the foil pouch.

Using your fingernail, lift one corner of the patch and peel the patch and the plastic off the foil liner.

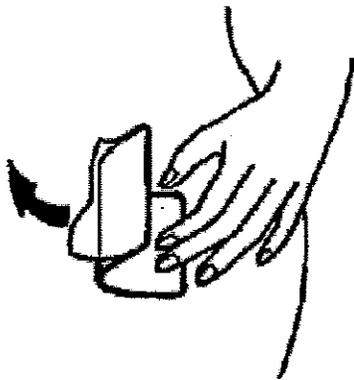


*Sometimes patches can stick to the inside of the pouch – be careful not to accidentally remove the clear liner as you remove the patch.*



6

Peel away half of the clear plastic and be careful not to touch the exposed sticky surface of the patch with your fingers.



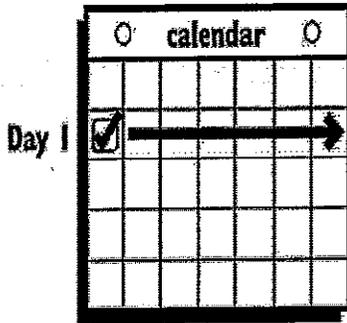
7

Apply the sticky side of the patch to the skin you've cleaned and dried, then remove the other half of the clear plastic.

Press firmly on the patch with the palm of your hand for 10 seconds, making sure the edges stick well.

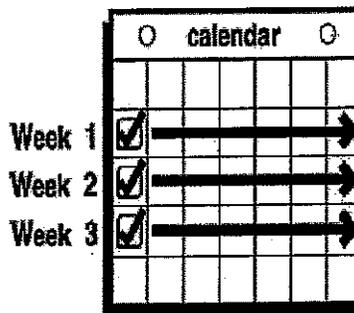
Run your finger around the edge of the patch to make sure it is sticking properly.

Check your patch every day to make sure all the edges are sticking.



8

Wear the patch for seven days (one week). On your 'Patch Change Day,' Day 8, remove the used patch. Apply a new patch immediately. *The used patch still contains some medicine – carefully fold it in half so that it sticks to itself before safely disposing of it in the trash. Used patches should not be flushed down the toilet.*

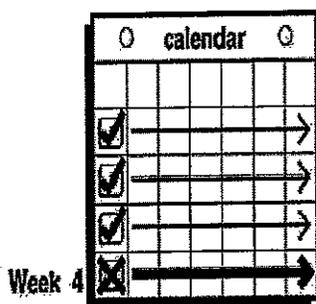


9

Apply a new patch for week two (on Day 8) and for week three (on Day 15), on your 'Patch Change Day.' *To avoid irritation, do not apply the new patch to the same exact place on your skin.*

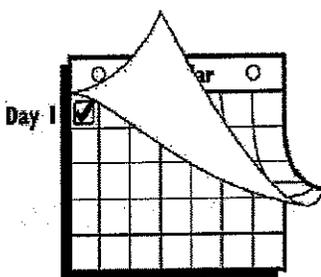
10

Do not wear a patch on week four (Day 22 through Day 28). *Your period should start during this week.*



11

Begin your next four week cycle by applying a new patch on your normal 'Patch Change Day,' the day after Day 28 – *no matter when your period begins or ends.*



**If your patch has become loose or has fallen off...**

- **for less than one day**, try to re-apply it or apply a new patch immediately. No back-up contraception is needed. *Your 'Patch Change Day' will remain the same*

- **for more than one day OR if you are not sure for how long**, YOU MAY BECOME PREGNANT – **Start a new four week cycle immediately** by putting on a new patch. *You now have a new Day 1 and a new 'Patch Change Day.'* You must use back-up contraception, such as a condom, spermicide, or diaphragm for the first week of your new cycle.
- do not try to re-apply a patch if it's no longer sticky, if it has become stuck to itself or another surface, if it has other material stuck to it or if it has previously become loose or fallen off. No tapes or wraps should be used to keep the patch in place. If you cannot re-apply a patch, apply a new patch immediately.

**If you forget to change your patch...**

- **at the start of any patch cycle,**

Week one (Day 1): If you forget to apply your patch, YOU COULD BECOME PREGNANT – *you must use back-up contraception for one week.* Apply the first patch of your new cycle as soon as you remember. *You now have a new 'Patch Change Day' and new Day 1.*

- **in the middle of your patch cycle,**

Week two or week three: If you forget to change your patch for **one or two days**, apply a new patch as soon as you remember. Apply your next patch on your normal 'Patch Change Day.' No back-up contraception is needed.

Week two or week three: If you forget to change your patch for **more than two days**, **YOU COULD BECOME PREGNANT** – **start a new four week cycle as soon as you remember by putting on a new patch.** *You now have a different 'Patch Change Day' and a new Day 1. You must use back-up contraception for the first week of your new cycle.*

- **at the end of your patch cycle,**

Week four: If you forget to remove your patch, take it off as soon as you remember. Start your next cycle on your normal 'Patch Change Day,' the day after Day 28. No back-up contraception is needed.

- **at the start of your next patch cycle,**

Day 1 (week one): If you forget to apply your patch, **YOU COULD BECOME PREGNANT** – apply the first patch of your new cycle as soon as you remember. *You now have a new 'Patch Change Day' and new Day 1. You must use back-up contraception for the first week of your new cycle.*

- *you should never have the patch off for more than seven days.*

#### **Other information**

- Always apply your patch to clean, dry skin. Avoid skin that is red, irritated or cut. Do not use creams, oils, powder or makeup on your skin where you will put a patch or near a patch you are wearing. It may cause the patch to become loose.
- Do not cut, damage or alter the ORTHO EVRA<sup>®</sup> patch in any way.
- If patch use results in uncomfortable irritation, the patch may be removed and a new patch may be applied to a new location until the next Change Day. Only one patch should be worn at a time.
- Some medicines may change the way ORTHO EVRA<sup>®</sup> works. If you are taking any medication, you must talk to your health care professional **BEFORE** you use the patch. *You may need to use back-up contraception.*
- Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).
- Single replacement patches are available through your pharmacist.
- For further information log on to **www.orthoevra.com** or call toll free **1 877 EVRA 888**

## **WHEN YOU SWITCH FROM THE PILL TO ORTHO EVRA®:**

If you are switching from the pill to ORTHO EVRA®, wait until you get your menstrual period. If you do not get your period within five days of taking the last active pill, check with your health care professional to be sure that you are not pregnant.

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### **IMPORTANT POINTS TO REMEMBER**

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1. **IT IS IMPORTANT TO USE ORTHO EVRA® exactly as directed in this leaflet.** Incorrect use increases your chances of becoming pregnant. This includes starting your contraceptive cycle late or missing your scheduled CHANGE DAYS.
2. You should wear one patch per week for three weeks, followed by one week off. **You should never have the patch off for more than seven days in a row.** If you have the patch off for more than seven days in a row and you have had sex during this time, **YOU COULD BECOME PREGNANT.**
3. **IF YOU ARE NOT SURE WHAT TO DO ABOUT MISTAKES WITH PATCH USE:**
  - Use a **BACK-UP METHOD**, *such as a condom, spermicide, or diaphragm* anytime you have sex.
  - Contact your health care professional for instructions.
4. Do not skip patches even if you do not have sex very often.
5. **SOME WOMEN HAVE SPOTTING OR LIGHT BLEEDING, BREAST TENDERNESS OR MAY FEEL SICK TO THEIR STOMACH DURING ORTHO EVRA® USE.** If these symptoms occur, do not stop using the contraceptive patch. The problem will usually go away. If it doesn't go away, check with your health care professional.
6. **MISTAKES IN USING YOUR PATCHES CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING.**
7. If you miss **TWO PERIODS IN A ROW** contact your health care professional because you might be pregnant.
8. The amount of drug you get from the ORTHO EVRA® patch should not be affected by **VOMITING OR DIARRHEA.**
9. **IF YOU TAKE CERTAIN MEDICINES, ORTHO EVRA® may not work as well.** Use a non-hormonal back-up method (such as condoms, spermicide, or diaphragm) until you check with your health care professional.

10. IF YOU WANT TO MOVE YOUR PATCH CHANGE DAY to a different day of the week, finish your current cycle, removing your third ORTHO EVRA<sup>®</sup> patch on the correct day. **During week four**, the “patch-free week” (Day 22 through Day 28), you may choose an earlier Patch Change Day by applying a new patch on the day you prefer. You now have a new Day 1 and a new Patch Change Day. **You should never have the patch off for more than seven days in a row.**
11. BE SURE YOU HAVE READY AT ALL TIMES:
  - A NON-HORMONAL BIRTH CONTROL method (such as condoms, spermicide, or diaphragm) to use as a back-up in case of dosing errors.
12. IF YOU HAVE TROUBLE REMEMBERING TO CHANGE YOUR CONTRACEPTIVE PATCH, talk to your health care professional about how to make patch-changing easier or about using another method of birth control.
13. Single replacement patches are available through your pharmacist.
14. For Patch replacement, see “How to use ORTHO EVRA<sup>®</sup>” section.

IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your health care professional.

#### **PREGNANCY DUE TO ORTHO EVRA<sup>®</sup> FAILURE**

The incidence of pregnancy from hormonal contraceptive failure is approximately one percent (i.e., one pregnancy per 100 women per year) if used correctly. The chance of becoming pregnant increases with incorrect use. If contraceptive patch failure does occur, the risk to the fetus is minimal.

#### **PREGNANCY AFTER STOPPING ORTHO EVRA<sup>®</sup>**

There may be some delay in becoming pregnant after you stop using ORTHO EVRA<sup>®</sup>, especially if you had irregular menstrual cycles before you used hormonal contraceptives. It may be best to postpone conception until you begin menstruation regularly once you have stopped using ORTHO EVRA<sup>®</sup> and want to become pregnant.

There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping hormonal contraceptives.

#### **OVERDOSAGE**

ORTHO EVRA<sup>®</sup> is unlikely to cause an overdose because the patch releases a steady amount of the hormones. Do not use more than one patch at a time. Serious ill effects have not been reported when large doses of oral contraceptives were accidentally

taken by young children. Overdosage may cause nausea and vomiting. Vaginal bleeding may occur in females. In case of overdosage, contact your health care professional or pharmacist.

### **OTHER INFORMATION**

Your health care professional will take a medical and family history before prescribing ORTHO EVRA<sup>®</sup> and will examine you. The physical examination may be delayed to another time if you request it and the health care professional believes that it is a good medical practice to postpone it. You should be reexamined at least once a year. Be sure to inform your health care professional if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your health care professional, because this is a time to determine if there are early signs of side effects of hormonal contraceptive use.

Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth control.

If you want more information about ORTHO EVRA<sup>®</sup>, ask your health care professional or pharmacist. They have a more technical leaflet called the Prescribing Information that you may wish to read.

### **Special Precautions for Storage and Disposal**

Store at room temperature.

Store patches in their protective pouches. Apply to the skin immediately upon removal from the protective pouch.

Do not store in the refrigerator or freezer.

Used patches still contain some active hormones. Fold each patch in half so that it sticks to itself before safely disposing of it in the trash. Used patches should not be flushed down the toilet.

### **(INSERT LOGO)**

ORTHO-McNEIL PHARMACEUTICAL, INC.

Raritan, New Jersey 08869

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# **Court's Exhibit C**



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## Assignments on the Web &gt; Patent Query

## Patent Assignment Abstract of Title

***NOTE: Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.***

**Total Assignments: 2**Patent #: [5876746](#)

Issue Dt: 03/02/1999

Application #: 08660024

Filing Dt: 06/06/1996

Inventors: JANAN JONA, JAY AUDETT, NOEL SINGH

Title: TRANSDERMAL PATCH AND METHOD FOR ADMINISTERING 17-DEACETYL NORGESTIMATE ALONE OR IN COMBINATION WITH AN ESTROGEN

**Assignment: 1**Reel/Frame: [008206/0642](#)

Recorded: 11/04/1996

Pages: 6

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors: [JONA, JANAN](#)

Exec Dt: 09/12/1996

[AUDETT, JAY](#)

Exec Dt: 09/16/1996

[SINGH, NOEL](#)

Exec Dt: 09/10/1996

Assignee: [CYGNUS, INC.](#)400 PENOBSCOT DRIVE  
REDWOOD CITY, CALIFORNIA 94063

Correspondent: MORRISON &amp; FOERSTER, L.L.P.

ANTOINETTE F. KONSKI

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PALO ALTO, CA 94304-1018

**Assignment: 2**Reel/Frame: [010668/0869](#)

Recorded: 03/07/2000

Pages: 7

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignor: [CYGNUS, INC.](#)

Exec Dt: 12/13/1999

Assignee: [ORTHO-MCNEIL PHARMACEUTICAL, INC.](#)P.O. BOX 300  
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RARITAN, NEW JERSEY 08869

Correspondent: JOHNSON &amp; JOHNSON

AUDLEY A. CIAMPORCERO, JR., ESQ.

ONE JOHNSON &amp; JOHNSON PLAZA

NEW BRUNSWICK, NJ 08933-7003

Search Results as of: 08/08/2007 03:43 PM

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## Assignments on the Web &gt; Patent Query

## Patent Assignment Abstract of Title

**NOTE: Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.**

## Total Assignments: 1

Patent #: [5972377](#)

Issue Dt: 10/26/1999

Application #: 09165526

Filing Dt: 10/02/1998

Inventors: JANAN JONA, JAY AUDETT, NOEL SINGH

Title: TRANSDERMAL PATCH AND METHOD FOR ADMINISTERING 17-DEACETYL NORGESTIMATE ALONE OR IN COMBINATION WITH AN ESTROGEN

## Assignment: 1

Reel/Frame: [010668/0869](#)

Recorded: 03/07/2000

Pages: 7

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignor: [CYGNUS, INC.](#)

Exec Dt: 12/13/1999

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## Patent Assignment Abstract of Title

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## Total Assignments: 1

Patent #: [6071531](#)

Issue Dt: 06/06/2000

Application #: 09340859

Filing Dt: 06/28/1999

Inventors: JANAN JONA, JAY AUDETT, NOEL SINGH

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# **Court's Exhibit D**

ORTHOMcNEIL  
Ortho Evra

**Ortho Evra**  
(norelgestromin/ethinyl estradiol  
transdermal system)

See patient instructions. Apply immediately upon removal from pouch. Each transdermal system is intended to be worn 7 days as prescribed.

Used patches should not be flushed down the toilet.

Package not child-resistant. Keep out of reach of children.

Do not store unpouched. Store at controlled temperature at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

Note your Patch  
Change Day here

- Sunday
- Monday
- Tuesday
- Wednesday
- Thursday
- Friday
- Saturday

Place RX Label Here

ORTHOMcNEIL

ORTHOMcNEIL PHARMACEUTICAL, INC.  
Raritan, New Jersey 08869

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10153700

Revised May 2006

U.S. Patent Nos. 5,876,746  
5,972,377; 6,071,531

# **Court's Exhibit E**

**MEDICINES ASSESSMENT ADVISORY COMMITTEE (MAAC)  
REPORT ON THE EVALUATION OF THE PRECLINICAL  
AND CLINICAL DATA OF A NEW MEDICINE APPLICATION**

**ASSESSOR:**

**COMPOUND:** Levonorgestrel

**PRODUCT:** EVRA

**DOSE FORM:** Transdermal Patch

**MOH FILE NUMBER:** TT50-7103

**STRENGTH:** Norelgestromin 6mg  
**(each patch)** Ethinyloestradiol 600mcg

**PROPOSED INDICATION(S):** Female contraception

**PROPOSED DOSAGE:** Each patch releases 150mcg norelgestromin and 20mcg ethinyl oestradiol every 24 hours.

One patch is applied every week for 3 weeks followed by a treatment-free week.

---

## **BACKGROUND**

Combined hormonal contraceptives have been available for over 30 years now and provide effective and acceptably safe contraception for women. This application is for a new combined oestrogen/progestogen transdermal patch, which has been developed to offer some advantages over daily oral dosing. The claimed benefits of this route of administration include greater compliance with dosing instructions; elimination of first pass metabolism and reduced likelihood of gastrointestinal disturbances interfering with contraceptive efficacy.

The active ingredients of the EVRA patch are ethinyl oestradiol (EE) and norelgestromin (17d-NGM). EE was synthesised in 1938 and has been licensed for many years in various products, but 17d-NGM has not previously been approved as the progestogen component of a contraceptive product. However, 17d-NGM is the primary active metabolite of norgestimate (NGM) which has been approved for use in combined oral contraceptive products (e.g. Cilest) in the EU.

## **WORLDWIDE REGULATORY STATUS**

EVRA was first licensed in the USA in November 2001, in Canada and Mexico in August 2002 and in 16 European countries (including Sweden and UK) also in August 2002.

### PART III - PHARMACOTOXICOLOGICAL (PRECLINICAL) DATA

The deacetylation of NGM to 17d-NGM occurs mainly in the oral absorption process as a first pass effect - therefore the applicant draws on the earlier preclinical assessment of NGM's oral safety to support this application for topically applied 17d-NGM.

One of the excipients in the patch - lauryl lactate - is also new to medicinal products (although it has had topical usage in cosmetic products) and its toxicity is also assessed in the application.

#### **A. Animal pharmacology**

##### **1 Pharmacodynamics**

The primary effect of EE + NGM/17d-NGM is anti-ovulatory, with both EE and NGM/17d-NGM having further pharmacological activity on the female reproductive system. Studies investigating these system-specific effects are described and also those investigating general pharmacological effects.

##### ***Anti-ovulatory activity***

**NGM/17-dNGM alone:** both subcutaneous and oral NGM and 17-dNGM had anti-ovulatory activity in rats, with SC administration being more potent. The SC dose of NGM required to inhibit ovulation in 50% of Sprague-Dawley rats was 0.22 mg/kg. In this study NGM was 0.18 times as potent as levonorgestrel. Further rat studies showed that NGM suppresses ovulation by inhibiting the release of LH at the hypothalamic-pituitary axis.

**NGM/17-dNGM + EE:** two studies in Sprague-Dawley rats showed that the combination of NGM/17-dNGM and EE showed greater inhibition of ovulation than NGM alone. A third study showed that NGM alone had the same effect as the combination.

##### ***Progestational activity***

NGM has progestational activity including endometrial proliferation, maintenance of pregnancy and progesterone receptor binding.

Endometrial proliferation was measured in NZ white rabbits - 17d-NGM and levonorgestrel were 1.4 and 4.9 times as potent as NGM (oral dosing) in this effect. In another study s.c. NGM was 0.35 times as potent as LNG and IM NMG was 0.5 times as potent. A further study investigated local application of NGM to one of the uterine horns where a near maximal response was observed, with no endometrial proliferation observed in the unexposed horn.

Maintenance of pregnancy was studied in ovariectomised Wistar rats. NGM given s.c. at 0.8mg/kg maintained 50% of the normal number of implant sites.

Progesterone receptor binding was studied *in vitro* using the endometrium of NZ white rabbits. NGM was shown to displace labelled progesterone from the receptors - i.e.

inhibiting formation of the progesterone/receptor complex. In these studies NGM was about 0.1 times as potent as LNG.

#### ***Oestrogenic activity of EE***

Papers published in 1969 and 1971 are cited which demonstrated that EE had the following oestrogenic effects: stimulation of vaginal cornification in spayed female mice, stimulation of uterine growth in immature mice and rats, *in vitro* affinity for oestrogenic receptors in the rabbit uterus and induction of RNA synthesis in rat uteri.

#### ***Oestrogenic and anti-oestrogenic activity of NGM/17d-NGM***

NGM was demonstrated to have low oestrogenicity in rat studies of vaginal cornification and uterine glycogen deposition. In addition, an *in vitro* study of oestrogen receptor binding showed no specific binding of NGM.

The anti-oestrogenic activity of NGM was also studied, as this might potentially counteract the oestrogenic properties of EE when used in combination. From vaginal cornification and uterotrophic activity studies in rats it was concluded that NGM/17d-NGM exerts anti-oestrogenic activity.

#### ***Oestrogenic and anti-oestrogenic activity of NGM/17d-NGM plus EE***

A further vaginal cornification study in Wistar rats showed that the combination of NGM and EE produced a two-fold increase in uterine weight and was 0.048 times as uterotrophic as EE alone (i.e. the combination had oestrogenic effects but much less than EE alone).

*Comment:* some of the increase in uterine weight might have been due to progestogenic effects in the uterus (e.g. glandular hypertrophy) in addition to oestrogenic effects.

The combination of NGM and EE was also shown to have anti-oestrogenic effects in rat studies, but this was less potent than NGM alone.

#### ***Androgenic and anti-androgenic activity studies***

Rat studies showed NGM was a very weak stimulator of ventral prostate growth. Rabbit studies showed that NGM failed to displace testosterone from human SHBG, which indicates weak or no affinity for SHBG (in comparison, levonorgestrel had potent affinity for SHBG). These studies showed that NGM/17d-NGM has low androgenic activity in these animal models.

Anti-androgenicity studies (ability to inhibit testosterone-stimulated growth of the ventral prostate in rats) showed NGM had no anti-androgenic activity.

Further rat studies of the androgenic effects of the combination (orally administered NGM + EE) showed a lower androgenic effect than NGM alone. NGM + EE did not have any anti-androgenic effects either.

### *General pharmacodynamic effects*

Oral administration of NGM to Sprague-Dawley female rats at doses up to 25mg/kg over 24 hours, showed no evidence of CNS or autonomic effects.

IV administration of NGM to dogs at 0.5 mg/kg did not produce significant changes in BP, heart rate, autonomic responses nor any inhibition of neuronal mechanisms. The expert believes these studies indicate that side effects such as orthostatic hypotension would be unlikely.

Animal pharmacodynamic studies of effects of NGM/17d-NGM on the respiratory system and GI tract have not been performed.

### **2. Animal pharmacokinetics**

A series of older (1970s) radio-labelled studies showed that oral NGM was well absorbed and then relatively slowly eliminated. Peak levels occurred within 2 to 6 hours of administration, with half-lives of 30 hours in the dog, 55 to 70 hours in the rat and 42 hours in the monkey. The co-administration of EE with NGM did not alter the rate of elimination in animals.

These studies also showed that 17d-NGM is the major metabolite of NGM and a further *in vitro* study suggested that NGM was extensively converted to 17d-NGM in the human liver and gut.

A series of more recent studies (post 1995) with unlabelled NGM and 17d-NGM have been performed in the rat, rabbit and rhesus monkey.

#### *Rat studies*

A single dose pharmacokinetic study in four rats demonstrated detection of 17d-NGM in serum where levels of NGM were mostly undetectable.

A 14 day oral study of NGM + EE (3 different doses of the combination) showed that 17d-NGM was the major analyte on both the first and final day of the study. NGM and 3-keto-NGM (the other metabolite of NGM) were only quantifiable after administration of the highest dose.

#### *Rabbit studies*

In a single dose IV (NGM 6mg/kg) study in female rabbits, mean plasma concentrations of NGM were over 30ng/ml for the first hour after dosing. At 20 minutes post-dose, concentrations of 17d-NGM were more than 5 times that of the parent drug and remained high for 3 hours after dosing.

In another rabbit study where NGM+EE was given orally to female rabbits, neither NGM nor 17d-NGM could be detected in the serum. This raised some doubts about systemic exposure to 17d-NGM in this species and therefore further studies were performed. Three further rabbit studies confirmed exposure to 17d-NGM – a study in pregnant rabbits which

showed accumulation after repeated dosing; and two studies in non-pregnant rabbits where patches containing various strengths of 17d-NGM + EE were applied in one-week exposure cycles. The patch studies showed that  $C_{max}$  was achieved at 24 hours after application and that serum levels of 17d-NGM and EE were essentially dose-proportional.

#### **Monkey studies**

The main Rhesus monkey study investigated serum concentrations of NGM and its metabolites after single and repeated oral doses of NGM + EE. A low dose and high dose regime of NGM + EE (daily oral dosing) were studied and  $C_{max}$  and  $AUC_{24hr}$  for NGM, 17d-NGM and 3-keto NGM were measured at 1 day and 21 days.

NGM was detected in some of the high-dose group only and 3-keto NGM was not detected in any samples from either dose group. 17d-NGM was detected and quantified, showing a dose-related exposure, but with no change in the concentrations during repeated administration.

#### **Distribution studies**

Distribution of 17d-NGM has not been studied directly, but studies of radiolabelled oral NGM showed extensive distribution of radioactivity to skin, muscles, liver, adrenals, and adipose tissue. Tissue levels declined after administration, indicating no significant retention.

A new protein binding *in vitro* study was performed to compare the binding of 17d-NGM in the female rat, rabbit, rhesus monkey and women. The results showed that plasma protein binding of 17d-NGM was about the same (98.8 - 99.1%) in all four species. This means that comparison of exposures between species can be based on total plasma concentrations and need not be corrected for the free fraction.

#### **Metabolism studies**

*In vitro* metabolism studies of 17d-NGM in rat hepatic S9 fractions showed that after 60 minutes, 85% of the test compound was intact and the other 15% had been hydroxylated. The *in vitro* studies suggested that norgestrel might be an intermediate metabolite of 17d-NGM. As norgestrel has progestogenic activity (it is an active ingredient in other contraceptive products) if it is present *in vivo* at significant levels, this may contribute significantly to the effects of 17d-NGM.

The pharmacokinetic studies in the rat and rabbit (described above) also measured serum levels of norgestrel and these results showed low levels which were unlikely to contribute progestogenic effects in these species. However, in the monkey studies the AUCs for norgestrel were more than twice those for 17d-NGM. The relevance of this for humans is discussed further in the clinical section.

## B. Toxicology

Again, preclinical data obtained with NGM in the development of Cilest is referred to in this application as oral NGM is metabolised to 17d-NGM. It is acknowledged that some of these studies were performed before the introduction of GLP, but many of the studies took place after GLP regulations came into effect.

Some new reproductive toxicology and mutagenicity studies have been done with 17d-NGM alone. There are also some local tolerance studies using the EVRA patch.

### Single dose toxicity studies

Studies in mice, rats and dogs have assessed acute toxicity after single oral doses of NGM and EE, either separately or in combination. Another study administered NGM + EE intravenously to dogs.

No toxic effects were noted in rats at doses up to 5,000 mg/kg oral NGM + EE. Transient behavioural signs were noted in mice (attributed to EE) but in dogs there were no significant findings.

### Repeat dose toxicity studies

Studies were performed in rats, dogs and monkeys given oral NGM or NGM + EE for 3 months to 10 years.

**Rat Studies** - up to 3 months of NGM alone, showed decreased serum cholesterol levels, decreased uterine weights, decreased ovarian weights and increased liver weights.

**Dog studies** - up to 3 months of NGM alone resulted in decreased serum cholesterol levels, decreased ovarian weight, decreased uterine weight with compact endometrium and cystic hyperplasia of the gall bladder mucosa. NGM + EE administration resulted in increased uterine weight (and cystic endometrial hyperplasia), decreased ovarian weight (with germinal epithelial cell proliferation and ovarian hyperplasia) and increased kidney weight.

**Monkey studies** - up to 3 months of NGM alone decreased the mean duration of menses and increased weights of liver and heart (without histological changes). NGM + EE also reduced the number and duration of menstrual cycles. In addition, the combination resulted in increased cervical mucous and mammary gland activity and endometrial sloughing was also observed.

### Chronic (> 3 months) oral toxicity studies

Longer-term studies were performed in rats, dogs and monkeys - although in his commentary on these studies, the expert cites references which claim the dog is not an appropriate species for assessing the safety of contraceptive steroids in humans.

All studies used oral NGM + EE. Lower doses were used in the long-term studies than in the 3-month studies "in order to avoid secondary effects due to the exaggerated pharmacological action observed in the 3-month studies".

**Rat studies** - a 2-year study reported endometrial hyperplasia, increased alkaline phosphatase levels, liver cell hyperplasia and various other changes thought to be progestogenic effects. An increased incidence of lenticular opacities could not be explained and so a second study was performed using dose levels lower than in the first study. In the second study there was no difference in the incidence of lenticular opacities in the treatment and control groups, but the time to onset of opacities was shorter in the treated animals.

The expert does not consider the finding of lenticular opacities in rats (or dogs) is relevant to humans as these effects have been reported previously in animal studies for other combined contraceptives, but have never been reported in women taking these contraceptives for many years.

**Dog studies** - a 2 year study treated dogs cyclically (21 days on followed by 7 days off) with NGM + EE. Treatment effects included absence of oestrus, increased weights of heart and liver, mammary tissue hyperplasia and gall bladder mucosal hyperplasia. Endometrial hyperplasia, inhibition of ovarian maturation and vaginal/cervical cornification and hyperplasia were also observed.

A 7-year study again used a cyclical regime, but with lower doses than the 2-year study. Similar changes were noted, but also a higher incidence of lenticular opacities in treated animals compared to controls.

**Monkey studies** - there are 3 long-term monkey studies presented. A 6-month study revealed 'expected effects' with the exception of a single case of an endometrial epithelial plaque in one animal. A two year study treated Rhesus monkeys with cyclical NGM + EE and treatment related effects included transient increases in prothrombin time, increased serum TGs and retinal hypopigmented foci. There were also some cases of liver changes including congestion and small haemorrhages.

A 10 year study, again using a cyclical regime of NGM + EE but with dose levels lower than in the 2 year study, was also performed. The monkeys menstruated during the withdrawal week and mammary secretions were observed in the higher dose groups. The following treatment effects were noted: hypopigmentation of the retinal macula (but no change in visual acuity), increased liver and pituitary weights, decreased ovarian weights, lobular hyperplasia of the mammary glands, increased incidence of multifocal myocardial fibrosis and a dose-related hypertrophy of the pars distalis of the pituitary gland.

#### **Dermal toxicity/local tolerance studies**

Three studies are described - an initial topical exposure study in rabbits, a 28 day dermal toxicity study and a dermal sensitization test in guinea pigs.

**Initial exposure test** - the first skin irritation test applied both patches with and without active ingredients to the shaved skin of rabbits for a single 24 hour exposure period. All patches were noted to be mildly irritating to the rabbit skin.

**A one month dermal toxicity study** was conducted in rabbits with active or placebo patches applied to shaved sites on each animal (2 new patches per animal per week) giving continuous exposure for 28/29 days. Three different size patches were tested (10, 15 or 20 cm<sup>2</sup>) with the active patches containing up to 6mg 17d-NGM and 0.75mg EE. These doses are said to represent 15 to 30 times the proposed human dosage based on a 50 kg woman.

Erythema and irritation were observed at the application site in all treatment and placebo animals and this was attributed to difficulty removing the patches. On necroscopy, microscopy of the skin patch showed superficial inflammation, occasional acanthosis and occasional haemorrhage.

There were also many changes to the reproductive tract noted at necroscopy, including uterine enlargement and smooth muscle hypertrophy in the cervix and vagina. All these changes were considered to be physiologically compatible with the progestogenic and oestrogenic effects of the active patches. These effects demonstrate good topical absorption of NGM and EE through rabbit skin.

**The guinea pig study** was designed to test delayed contact hypersensitivity of a 17d-NGM + EE patch. Active, placebo or positive control patches were applied for six-hour periods, three times a week for 3 weeks at the same site. All positive control animals exhibited sensitisation responses. Neither patches with or without the active ingredients showed evidence of contact sensitisation in the guinea pig.

#### **Toxicity of Lauryl Lactate**

The excipients in the EVRA patch have all been used previously in other types of patches with the exception of lauryl lactate. The supporting evidence regarding the local toxicity of lauryl lactate includes:

- The dermal toxicity studies described above
- Eye and skin irritation studies were also performed by the supplier - LL was non-irritating to the eye and minimally irritating to rabbit skin

Systemic toxicity was tested in a single oral dose study in rats given 5ml/kg 10% LL in propylene glycol. No toxic effects were noted. The 28-day rabbit dermal toxicity study also showed no toxicity in rabbits after weekly application of the placebo patch for 4 weeks.

Other studies have shown LL does not have mutagenic potential. Two further studies - one *in vivo* using direct application of LL and one *in vitro* - are still ongoing.

## **Reproductive toxicity**

Five rat and rabbit studies are described which investigated the reproductive toxicity of NGM + EE. Effects on fertility included dose-related suppression of fertility, decreased implantation efficiency, decreased litter size and increased fetal resorption. These are all expected findings.

One rat study showed an unexpected increase in "wavy ribs" in the highest dose treatment group, but it is claimed this is a skeletal variant in rats (which is reversed after birth) rather than a teratogenic effect.

Another rat study administered NGM + EE through to day 21 of lactation to study perinatal toxicity. The highest dose group (0.6 mg/kg/day) showed significantly decreased offspring viability from birth to weaning and depressed pup weight.

As rabbits dosed orally with NGM are thought to be exposed to little/no 17d-NGM, a new rabbit study has been performed with 17d-NGM administered subcutaneously. This study demonstrated maternal toxicity - reduction in food consumption and thickened placentae - at higher doses (4-6 mg/kg/day). These doses also resulted in fetal malformations including cleft palate and paw hyperextension. Doses of 2mg/kg/day in the rabbit (which give an AUC approx 70 times that in humans using EVRA) were considered to be non-teratogenic, although an increase in fetal variations (e.g. reduced ossification) were seen at this dose level.

## **Mutagenic potential**

The Ames test with NGM and NGM + EE and the HGPRT test in Chinese Hamster Ovary cell lines exposed to NGM did not reveal any mutagenic activity. Chromosome aberration studies were also performed with NGM and NGM + EE. None of these showed mutagenicity but in one rat study there was a reduction in the ratio of polychromatic erythrocytes to total erythrocytes. This was thought to be an effect of repeated high dose NGM on erythropoiesis.

Four new studies were performed using 17d-NGM - the Ames test, the HGPRT test in Chinese Hamster Ovary cell lines, a chromosome aberration test (in human lymphocytes from female donors) and the micronucleus test. None of these tests demonstrated any mutagenic potential.

Reference is made to published studies which have demonstrated that EE increases chromosomal aberrations and chromatid exchanges in human lymphocyte cultures, but it is concluded that EE alone is not mutagenic.

## **Carcinogenicity**

The long-term studies of NGM + EE in rats, dogs and monkeys (outlined above) were used to study carcinogenic potential. The findings can be summarised as follows:

2-year rat study:	Non-significant increase in incidence of mammary neoplasms in treated group. Significant increase in mammary adenocarcinomas in high dose group.
2-year dog study:	One mammary ductal adenoma (benign) in one high dose dog
7-year dog study:	Leiomyomas or leiomyofibromas in 8 treated animals vs 1 control One high dose dog had uterine leiomyosarcoma.
10-yr monkey study:	Single occurrences of neoplasms in the vagina (leiomyoma) cervix (adenocarcinoma) thyroid (tubular adenoma) bladder (papilloma) intestine (leiomyoma) were observed. There were also 3 mammary gland tumours (2 in one animal) and a 'few miscellaneous neoplasms' of the skin, muscle, fat and pituitary gland.

Comment is made that these findings were either expected (rat studies) not relevant (dog studies) or coincidental findings (monkey studies). It is concluded that NGM does not have carcinogenic potential.

It is noted that literature reviews have shown that EE increases the incidence of pituitary tumours, malignant mammary tumours and uterine/cervix tumours in mice. In rats it is established that oestrogens cause mammary neoplasia and increase the incidence of benign liver tumours.

#### C. Summary of the Pharmacotoxicological Data

This is a comprehensive pharmacotoxicology submission largely based on studies of oral NGM. The animal pharmacokinetic studies demonstrated that oral doses of NGM are extensively metabolised to 17d-NMG soon after administration. This justifies the use of pharmacodynamic and toxicology studies which were performed during the development of oral contraceptive products containing NGM and EE.

The long term toxicology studies were all performed with oral NGM and perhaps strictly speaking, these should all have been performed with topically applied 17d-NGM + EE. The applicant has performed additional local tolerance/toxicity studies to support this application, but one weakness is that the longest of these was 28 days duration.

In other respects the applicant has performed new studies where appropriate (e.g. mutagenicity) and the results are reassuring. Most of the observations in the pharmacotoxicology studies would be expected from previous animal work on steroid hormones. The occasional unexpected finding has been discussed by the expert and it appears that no new major safety issues have arisen from the preclinical data presented in this application.

**PART IV - CLINICAL DATA**

**A. Clinical Pharmacology**

**1. Pharmacodynamics**

As demonstrated in the animal studies, the active ingredients of EVRA have both specific (i.e. reproductive system) and more general pharmacodynamic effects.

The reproductive effects include suppression of ovulation and effects on cervical mucus and the endometrium.

**Ovarian Suppression Studies**

The effects on ovarian function were determined primarily by measurement of serum progesterone and ovarian ultrasound, but LH and serum oestradiol were also measured.

**Study CONT-001:** Comparative trial of 3 different patch sizes (10cm<sup>2</sup>, 15cm<sup>2</sup> and 20cm<sup>2</sup>) with Cilest (OC containing norgestimate + EE). The patches had the following active ingredients:

Patch size	Total drug content	Anticipated daily dose
10cm <sup>2</sup>	3 mg 17d-NGM + 0.38 mg EE	125 mcg 17d-NGM + 13 mcg EE
15cm <sup>2</sup>	4.5 mg 17d-NGM + 0.56 mg EE	187 mcg 17d-NGM + 17 mcg EE
20cm <sup>2</sup>	6 mg 17d-NGM + 0.75 mg EE	250 mcg 17d-NGM + 25 mcg EE

150 patients were randomised to each of the four groups and progesterone levels were measured on days 7, 14, 21 and 28 of cycles 1, 3 and 4. A sub-group of 25 women per group had ovarian ultrasound (and serum LH & oestradiol measurements) to assess pituitary-ovarian activity. Both the 10cm<sup>2</sup> and 15cm<sup>2</sup> patch were associated with a higher incidence of ovarian follicles 20mm or greater than the 20cm<sup>2</sup> patch (EVRA) or Cilest. No ovarian follicles >30mm were observed in women using EVRA. Only the 20cm<sup>2</sup> patch (EVRA) achieved the pre-determined objective that the percentage of patients who ovulated should be significantly less than 15% and this result was similar to that seen for Cilest in this study.

**Study CONT-008:** Comparative trial of EVRA patch versus three oral contraceptives to assess ovarian suppression. 136 patients were randomised - 56 to EVRA groups (27 in group I and 29 in group II) 25 to Trinordiol, 28 to Tricilest and 27 to Alesse. The primary endpoint was follicular development, measured by ultrasonic assessment of maximum mean follicular (MMF) diameter over 5 cycles. The first three cycles were normal dosing cycles (3 weeks on and one week off treatment) and the MMF diameters in the EVRA group were significantly smaller in the EVRA group than either the Trinordiol or Alesse groups.

In cycle 4, 22 subjects continued to use EVRA for 10 days and 21 women used EVRA for seven days followed by 3 days of non-dosing. Following these 'dosing errors' the mean MMFs in both the EVRA sub-groups remained significantly smaller than either the Trinordiol or Alesse groups.

## **Cervical mucus and Endometrial effects**

**Study CONT-007:** Comparative trial of EVRA patch versus two different OCs to determine effects on cervical mucus and the endometrium. The aim was to enrol 20 subjects in each of the three treatment groups who would be studied for 3 treatment cycles (each 28 days). 45 women actually received the study drug with an average of 15 women per group. Quality of cervical mucus was assessed at days 7 and 14 of cycles 1 and 3. The results showed no significant difference in the quality of cervical mucus between the EVRA and the OC groups.

This study also examined endometrial effects, as endometrial biopsies were performed on days 7 and 14 of cycles 1 and 3. Women in all three groups had 'progestational' (thin and non-secretory) endometrium at these times - as would be expected in those taking combined hormonal contraceptives.

### **Endocrine effects**

Study CONT-008 also measured several endocrine parameters in women using Cilest (and those taking one of the 3 COCs in the study). FSH, LH, DHEA-S, oestradiol and progesterone showed a pattern indicating suppression of the hypothalamic-pituitary axis which was similar for EVRA and the 3 COCs.

Other endocrine changes for all 4 products included raised thyroxine binding globulin (TBG) and total thyroxine, raised SHBG and corticoid binding globulin. There was also a slight decrease in total and free testosterone, but no change in prolactin levels.

### **Effects on lipids**

Study CONT-005 examined the effects of EVRA (compared to placebo patch) on lipid profiles over 9 cycles of treatment. At cycles 3, 6 and 9 the EVRA group had greater mean increases from baseline for several lipid parameters including HDL, LDL, total cholesterol and total TGs compared to placebo. The calculated LDL/HDL ratio showed a favourable decrease for EVRA and an unfavourable increase for placebo - however the difference (in mean change in the ratio from baseline) between EVRA and placebo was not significant. Previous studies of lipid profiles with Cilest showed similar results to these studies of transdermal 17d-NGM.

### **Carbohydrate parameters**

Study CONT-006 showed no changes in mean fasting blood glucose levels during EVRA treatment and no difference between EVRA and the two COCs studied. A previous study showed a modest increase in serum glucose one-hour post dosing in a GTT performed after 6 cycles of Cilest.

### **Effects on coagulation**

Study CONT-006 also examined the effects of EVRA of several blood coagulation parameters. EVRA increased the conversion of prothrombin to thrombin and resulted in raised levels of FDPd-d (protein formed when clots are dissolved by fibrinolysis). In this study Mercilon & Triphasil also showed these effects which are consistent with the known effects of COCs.

## 2. Pharmacokinetics

The applicant cites pharmacokinetic studies performed with Cilest (oral norgestimate + EE) which demonstrated that 17d-NGM and norgestrel (NG) are formed during the absorption of oral norgestimate. After single or multiple doses of Cilest, serum concentrations of 17d-NGM and NG (and EE) were measurable, but levels of NGM and 3-keto NGM in all the samples analysed were below the limit of quantification (<0.1 ng/ml). Although both 17d-NGM and NG are formed from NGM, it was concluded that 17d-NGM is primarily responsible for the progestogenic activity of Cilest because NG is highly bound to SHBG which reduces its contribution to the activity. The half-life of 17d-NGM was approximately 25 hours (+/-9hrs).

Results are available from 9 pharmacokinetic studies and one pharmacodynamic study carried out with EVRA. The target concentrations for steady state serum concentrations of 17d-NGM and EE were those which covered 90% of the subjects in the PK studies for Cilest (because these levels are associated with clinically effective contraception). For 17d-NGM these were 0.6-1.2 ng/ml and for EE these were 25-75 pg/ml.

The ten studies were as follows:

**PH1-001** Pilot study using patch containing 6mg 17d-NGM and 0.6mg EE applied to the buttock. Mean steady state concentrations of EE were claimed to be below the target range and so EE was increased to 0.75mg for all other studies. However, a figure summarizing the results from this study shows that serum EE levels reached the target range at 24 hours and were maintained at about 30pg/ml until 168 hours (7 days) after which the levels fell out of the target range.

**PH1-003** This tested a 20cm<sup>2</sup> patch containing 6mg 17d-NGM and 0.75mg EE applied to the abdomen. 18 women completed the protocol and blood sampling was continued through 13 days. By 48 hours after application, both serum levels of 17d-NGM and EE had reached the target ranges which were maintained until 7 days when levels declined sharply. Interestingly, the results appear very similar to those for study PH1-003 where a higher dose of EE was used. Overall, steady state concentrations were lower than expected (although still in the target ranges) suggesting poorer absorption from the abdomen than from the buttock.

**PH1-004** This tested a single application of the above patch to four different sites -- abdomen, upper arm, upper torso or buttocks. 36 women successfully completed two or more treatments. The study demonstrated serum levels in the target ranges for all four sites and confirmed absorption from the abdomen was lower than from the upper arm, upper torso or buttocks.

**PH1-014** This was a randomised cross-over design study which assessed the pharmacokinetics of EVRA (single application to abdomen or buttock) relative to a one hour IV infusion of 252mcg 17d-NGM and 25mcg EE. The IV doses were calculated to correspond to the maximum exposures from oral Cilest if it were 100% bioavailable.

Absorption from the buttock was again shown to be higher than from the abdomen. An average systemic absorption was calculated from the buttock/abdomen results - 150mcg/day of 17d-NGM and 20mcg/day of EE.

**PH1-006** This tested 3 different patch sizes (10cm<sup>2</sup>, 15cm<sup>2</sup> and 20cm<sup>2</sup>) with 28/29 women in each group. The results showed that the most satisfactory steady state concentrations of both 17d-NGM and EE occurred with the 20cm<sup>2</sup> patch (containing 6mg 17d-NGM + 0.75mg EE). In this group only 1 subject (3%) had EE levels below the target range and 3 subjects (10%) had below the target range of 17d-NGM. Serum concentrations of 17d-NGM, NG and EE for the three patches were related to patch size.

**PH1-015** Effects of different environmental conditions on the release of 17d-NGM and EE from EVRA were tested. 30 women were randomised to different sequences of normal activity, sauna (10 mins), spa-pool (10mins) cold water bath (up to 30 mins), and treadmill (20-30 mins). The different activities did not affect 17d-NGM and NG kinetics, but the sauna, spa-pool, treadmill or combination of these increased both steady state and AUC of EE (although serum concentrations remained in the target range).

This study also investigated any possible diurnal variation in serum levels of 17d-NGM or EE. There were no consistent intra-individual variation in serum levels over a 24-hour period.

**PH1-005** Sequential application of EVRA (applied to the abdomen) for 2 consecutive weeks in 12 women. The mean steady state concentrations for both 17d-NGM and EE were slightly higher in week 2 relative to week one, but levels in both weeks were within the target ranges.

This study also examined serum levels during the interval when the patch was changed and showed slight decreases in serum concentrations of 17d-NGM and EE when the first patch was replaced (immediate replacement advised), although concentrations remained in the target ranges. When the second patch was left in place beyond 7 days, serum concentrations remained in the target ranges for 3 days of extended use.

**PH1-013** Sequential applications of EVRA (applied to either the abdomen or buttock) for 3 cycles (1 week each cycle) followed by a patch-free week. Serum levels of 17d-NGM and EE were similar in week 3 to week 1 and remained in the target ranges with little or no accumulation.

**PH1-017** Comparative studies of EVRA and 3 oral contraceptive pills as follows:  
i) One cycle of EVRA (3 patches, 7 days each) vs triphasic combined OC for 21 days.  
ii) One EVRA patch vs 7 days Allesse  
iii) One EVRA patch vs 7 days Mercilon

The intention of this study was to compare serum concentration profiles, but it is stated that the dosage periods, especially for the latter 2 groups, were too short to achieve steady states. Thus no results from this study are available.

**CONT-001** This pharmacodynamic study (see above) also measured serum levels of 17d-NGM, NG and EE during steady state following application of three different patch

sizes and after daily oral dosing of Cilest. Only the 20cm<sup>2</sup> patch (EVRA) produced similar (but slightly lower) levels of 17d-NGM, NG and EE to Cilest. There does not appear to have been any formal bioequivalence calculation from the results of this study.

#### **Metabolism and Excretion**

No new studies have been performed as it is considered that the metabolism of NGM was fully studied for the Cilest application. The Cilest studies have been briefly summarised. *In vitro* studies showed that the initial formation of 17d-NGM from NGM occurs in the cells of the gut wall, with further deacetylation occurring in hepatic cells. *In vivo* studies indicated that this metabolism of NGM in both the intestinal mucosa and the liver is effectively complete following oral absorption, so that little or no NGM is detectable in serum samples. Other studies indicated that 17d-NGM is metabolised predominantly by liver microsomal enzymes. Studies in human liver microsomes also showed a secondary hydrolysis to form norgestrel (NG).

Further studies using radio-labeled NGM showed that about 47% was excreted in the urine and 37% was excreted in the faeces over a 2-week collection period.

#### **Protein Binding studies**

The studies referred to are those performed for Cilest, which showed 17d-NGM is highly protein bound to albumin and NG is highly bound to SHBG. The strong affinity of NG for SHBG means it forms a complex which only dissociates slowly.

#### **Drug Interaction studies**

*In vitro* CYP450 studies performed for Cilest showed that the levels of 17d-NGM were low enough to suggest a low potential for a clinical interaction. However drugs which induce liver enzymes may increase the metabolism of EVRA and thus lower its contraceptive efficacy - as is known for COCs.

Study PH1-012 investigated the potential of oral tetracycline to interfere with the pharmacokinetics of 17d-NGM + EE. Tetracycline 2g/day (in 4 divided doses) were given 3 days before and 7 days during the application of EVRA. AUC and steady state serum concentrations of 17d-NGM + EE were not significantly different with or without tetracycline (bioequivalence 80-125% demonstrated).

No other interaction studies were performed and data-sheet warnings are largely based on those for COCs (see section below).

#### **Missed-patch PK simulation studies**

In an attempt to predict dosing irregularities with EVRA, a pharmacokinetic simulation was carried out. This showed that wearing the patch for up to 11 days (i.e. 4 days beyond recommended 7 days) would still give serum levels of 17d-NGM and EE in the target ranges. Changing the patch every 3-4 days would also result in levels in the target ranges.

The simulation also showed that lengthening the patch-free interval (beyond 7 days) at either the beginning or end of the cycle would result in sub-therapeutic serum concentrations of 17d-NGM and EE.

In addition, during the 3-week treatment period, not wearing a patch for one day would result in serum levels falling to below the target ranges and two or three days without a patch would result in levels significantly below the therapeutic range. Patches missed for more than one day, when replaced would not return into the therapeutic range for more than 24 hours.

**Comment:** it must be noted that, whilst quite a useful exercise, the results of this simulation have not mostly not been verified by clinical trials. The claim that adequate serum levels would be maintained for up to 11 days without changing the patch are not supported by some of the PK studies which showed serum levels fall off rapidly after 7 days.

#### *Comments on Pharmacokinetic studies*

The PK studies established that the 20cm<sup>2</sup> patch (6mg 17d-NGM + 0.75mg EE and henceforth known as EVRA in the application) produced target serum levels of both 17d-NGM and EE which are consistent with those produced by Cilest. The pharmacodynamic studies also established that these levels produced adequate ovarian suppression, again comparable to the COC Cilest. However, the first study which used a lower dose of EE (0.6mg) also produced serum EE levels in the target ranges and it is unclear why the dose was increased for the remaining studies. The higher dose may have been selected to allow for the lower absorption from abdominal application.

### **B. Clinical experience**

#### **i. Clinical studies**

Three pivotal phase three clinical trials were performed and on the basis of the results from the PK studies, the test patch in all three studies was 20cm<sup>2</sup> with a total drug content of 6mg 17d-NGM and 0.75mg (or 750mcg) EE. The 3 pivotal studies were as follows:

- CONT-002**      Open label non-comparative study of EVRA in 1664 women.  
Multicentre study in 73 centres in Europe, US, Australia and Israel
- CONT-003**      Open label randomised comparative study of EVRA vs Mercilon COC  
861 women randomised to EVRA vs 656 women to Mercilon  
Multicentre study in 65 centres in Europe and South Africa
- CONT-004**      Open label randomised comparative study of EVRA vs Triphasic COC  
856 women randomised to EVRA vs 639 women to Trinordiol  
Multicentre study in 45 centres in Canada and the US

The inclusion criteria were similar for all three studies: healthy, sexually active women age 18-45, with no contraindications to COCs and regular menstrual cycles. The participants were required to agree to use only the study drug as contraception, but could use other

contraceptives (presumably barrier methods) "when back-up contraception or protection against STDs was required".

### Efficacy results

In all three studies the primary efficacy endpoint was the incidence of pregnancy, calculated as both the Pearl Index (pregnancies per 100 women-years) and by life table analysis (probability of pregnancy over time of using contraceptive method) as recommended in the CPMP guideline. Other endpoints were compliance with treatment, completion of treatment and cycle control.

For the efficacy analyses pregnancies occurring both pre-treatment (estimated date of conception prior to study even if woman received study medication) and post-treatment (date of conception post-study) were excluded. Of 3,330 women who received study medication, a total of 3,319 women using EVRA for 22,155 cycles were evaluable for efficacy. The results are summarised in the table below:

	CONT-002 EVRA	CONT-003 EVRA vs Mercilon	CONT-004 EVRA vs Trinordiol
Number randomised or enrolled	1754	861 vs 656	856 vs 639
Number received study drug	1672	846 vs 643	812 vs 605
Overall pregnancies on therapy (n)	6	4 vs 2	5 vs 7
Overall Pearl Index	0.71 (0.14-1.28)	0.88 (0.02-1.74) vs 0.56 (0.0-1.33)	1.24 (0.15-2.33) vs 2.18 (0.57-3.8)
PI method failure*	0.59 (0.07-1.11)	0.66 (0.0-1.4) vs 0.28 (0.0-0.83)	0.99 (0.02-1.96) vs 1.25 (0.02-2.47)
Overall probability of pregnancy (life table) through 13 cycles	0.7%	0.5% vs 0.3%	1.3% vs 1.8%
Proportion completing treatment	72%	80% vs 86%	70% vs 76%

\* on-therapy 'method failures' were defined as pregnancies occurring when (as far as was known) the subject had complied with dosing

The results show that EVRA has good contraceptive efficacy with an overall Pearl Index for all 3 studies = 0.88 (0.43-1.32). In the comparative studies EVRA was less effective than Mercilon but more effective than Trinordiol. Overall the risk of pregnancy through 13 cycles was similar between EVRA and either COC.

So-called 'exploratory' analyses were performed on the results from the above studies to determine if age, weight, race, smoking or site of application were associated with contraceptive efficacy. The only association found was with weight - 5 of the 15 (one third) pregnancies in women using EVRA occurred in women with a baseline weight of 90kg or greater.

### Compliance and completion

In the two comparative studies, compliance with using EVRA was better than with the COCs. In study 003 perfect compliance in each cycle ranged from 90%-97% in the EVRA group and 85%-92% in the Mercilon group. There were no dosing errors in 97% EVRA cycles compared with 91% Mercilon cycles. In study 004 compliance was 86%-95% in the EVRA group compared with 76%-86% in the Trinordiol group. There were no dosing errors in 95% of cycles in the EVRA group compared with 81% in the Trinordiol group.

In each study two thirds of the participants were treated for 6 cycles and one third continued for 13 cycles. Although women using EVRA showed better compliance with treatment, fewer women using the patch completed the comparative studies (see table above).

### Cycle control

The primary endpoint for evaluation of cycle control in each study was the incidence of breakthrough bleeding/spotting at cycle 3. The results were as follows:

Study Number	Incidence of BTB/spotting at cycle 3
CONT-002	11% (range in each cycle = 5%-18%)
CONT-003	14 % EVRA vs 15% Mercilon
CONT-004	10% EVRA vs 9% Trinordiol

The mean duration of menses (i.e. withdrawal bleed at end of cycle) was 4-5 days. This was significantly longer (by one day) in women using EVRA compared to those using either Mercilon or Trinordiol. However, the lab data showed no decrease in haemoglobin from baseline to the end of the study.

### *Comments on pivotal clinical studies*

It should be noted that the marketed product EVRA contains 6mg 17 $\beta$ -NGM and 600mcg EE. Therefore none of the pivotal trials used the dose of EE in the marketed product, but used a product with a higher dose of oestrogen (750mcg EE).

Whilst the three pivotal studies appear to be well conducted there are some weaknesses which might affect the generalisability of the above results to other populations.

### Previous use of hormonal contraception

The majority of women recruited to these studies were using oral hormonal contraception in the two months before the study and 63% began EVRA without any interruption to their previous contraceptive therapy. These women may differ from new users of hormonal contraception in that ovulation has already been suppressed prior to the start of the EVRA study. This might therefore result in an over-estimate of the efficacy of EVRA in these trials. Another factor is that in such a population, users of COCs who experience serious or

severe adverse reactions are likely to have been eliminated prior to the EVRA study. This may result in the safety of EVRA appearing to be better in these trials than how it would be in 'real life' use where many women will be new users.

#### **Lack of blinding and use of back-up contraception**

The two comparative studies were open-label and there was no blinding to either the women or the investigators regarding the type of treatment administered. The applicant has argued that the dosing would have been too complicated if placebo patches and pills had been used in order to blind these studies. Whilst this may be true, it must be recognised that knowledge of treatment even in a randomised trial might affect the results. For example, those randomised to the patch may have had some doubts regarding its effectiveness (knowing it was a new product etc) and thus might have used more 'back-up' contraception just in case. Additional use of condoms etc was not recorded or studied in these trials and so it is not known if there were differences between the groups. Greater use of barrier methods in the EVRA group might overestimate the efficacy of the patch.

#### **Exploratory analyses**

The 'exploratory' analyses to determine risk factors for pregnancies must be treated with caution as the overall number of pregnancies was small (15). Whilst the observation regarding weight over 90kg being associated with one third of the pregnancies is interesting and suggests a relationship, it cannot be regarded as conclusive.

#### **Safety data**

In the three pivotal studies 3,330 women received at least one dose of EVRA. However, after exclusions and those who withdrew from the studies prematurely (26%) the numbers remaining on therapy were much lower. Only 643 women received EVRA for one year and there are no data beyond 14 cycles of treatment.

Of the 3,330 women in the safety analysis, 2,665 (80%) reported at least one treatment-emergent adverse event. The most frequently reported adverse events reported with EVRA were breast symptoms (discomfort, engorgement and pain) 22%, headache 21%, application site reaction 17% and nausea 17%.

**Breast symptoms** were more common in women using EVRA than those using Mercilon (25% vs 9%) and compared to Trinordiol (19% vs 6%). Nausea was also more common with EVRA than Mercilon (12% vs 6%) but similar to Trinordiol (20% vs 18%).

**Application site reactions** occurred in 17 % of EVRA users overall (range from 14-20% in pivotal studies). These were reported to be mild to moderate and this was not a common reason for discontinuation of EVRA. About 2% of patches fell off during treatment.

**Serious adverse events** – one woman using EVRA and one using Trinordiol died from suicide during the study. The Trinordiol patient experienced depression that was considered possibly related to the study drug, but the other suicide was thought to be unrelated.

50 women who received EVRA in the pivotal studies experienced one or more serious adverse events. Of these, 12 women had 14 serious events thought to be related to the medication including breast neoplasm (2) pulmonary embolus (2) endometriosis (1) menorrhagia (1) pain (1) hypoesthesia (1) paresthesia (1) migraine (1) arterial leg thrombosis (1) carcinoma-in situ cervix (1) increased intracranial pressure (1) and depression (1).

The incidence of serious adverse events was similar for EVRA and Mercilon (1.7% vs 2%) and for EVRA and Trinordiol (2% vs 1.8%).

#### **Risk of thrombo-embolism**

In the 3,330 women who took EVRA in the pivotal studies there were 7 possible venous thrombo-embolic events. Two of these were confirmed PEs but the applicant considers only one is associated with EVRA, as the other woman underwent a surgical operation the day after stopping EVRA. The remaining 5 appear to have been diagnosed with thrombophlebitis although 3 of these were treated with a 'heparin-like' medication.

*Comment:* The applicant has interpreted these data as a risk of VTE of 1 per 1,706 women years of treatment (22,176 cycles in the pivotal trials). However, it may be as high as 5 or even 7 per 1,700 women-years. These figures equate a several fold higher risk than that now accepted for third generation OCs (about 3 per 10,000 women/year).

#### **Discontinuations for adverse events**

399 (12%) of the 3,330 women given EVRA discontinued due to adverse events. The most common treatment limiting events were application site reaction, breast symptoms, nausea and headache.

In study CONT-003, 10% EVRA users discontinued due to adverse events compared with 5% of Mercilon users. In CONT-004 13% EVRA users discontinued due to an AE compared with 6% of Trinordiol users. These higher rates were not only due to application site reactions, but also due to nausea and breast symptoms.

#### **Sub-group analyses by age, race and weight**

The adverse events in the 3 pivotal studies have been analysed to try and determine in age, race or weight were risk factors for side effects. Whilst there was a suggestion that those experiencing AEs tended to be younger, the numbers were not sufficient for any of these sub-group analyses to be conclusive.

#### **Safety data from other studies**

The applicant has also included all the safety data from the 'supportive' studies which include the pharmacodynamic and PK studies for EVRA. In summary, the commonest adverse events were similar to the pivotal studies: headache, breast symptoms and nausea. In some studies the incidence of breast symptoms was as high as 41% (CONT-005) and headache as high as 39% (CONT-008). In one study application site reactions occurred in

39% of women. Other frequently reported events were intermenstrual bleeding (between 9-35% EVRA users) flu-like symptoms and respiratory tract infections.

## 2. Post-marketing experience

Although approved in the US in 2001 and in Europe in 2002 the applicant states that EVRA is not currently marketed in any country. There is thus no post-marketing data on this product.

## C. Summary of the clinical data

The efficacy data from the three clinical trials (in which 3,330 women used EVRA) show that this patch had similar efficacy to combined oral contraceptive pills. The overall Pearl Index for these one-year studies was 0.9 pregnancies/100-woman-years. There was a suggestion that efficacy might be decreased in heavier women, but the numbers of pregnancies were too small to give definitive results.

The safety data showed a significantly higher incidence of breast symptoms and nausea with the EVRA patch than with COCs. These side effects frequently lead to discontinuation of EVRA. The incidence of application site reactions was also high (up to 39% users) but these were less likely to lead to discontinuation.

The incidence of thrombo-embolic events in these studies was higher than that accepted for second or third generation COCs.

There are no efficacy or safety data beyond one year of use.

## DATA SHEET [OR SUMMARY OF PRODUCT CHARACTERISTICS]

Generally the data sheet is satisfactory, although much of it is just copied from the data-sheets/SPCs for COCs. The following areas need addressing:

- **Clinical trials description**

This is too long/detailed and gives too much emphasis to sub-group analyses (e.g. the efficacy and weight issue) implying the data are more conclusive than they are.

- **Precautions**

The data-sheet for EVRA states '*there is no clinical evidence indicating that a transdermal patch is in any aspect safer than combined oral contraceptives*'. However, the data reviewed in this application suggest that the patch is less safe than COCs. The higher incidence of breast symptoms, nausea etc shown in the two comparative clinical trials should be stated. It should also be emphasised that the risk of long term adverse events (e.g. breast cancer) is unknown with this product.

- **Thrombo-embolic disease**

The warnings included are those for COCs. There is no reference to the high incidence of VTE observed in the clinical trials for EVRA and it only states 'it is not yet known how EVRA influences the risk of VTE compared with COCs'.

- **Adverse reactions**

This section is so lengthy that it is almost impossible to determine which of the numerous events listed are relevant or possibly related to the product. In addition the description of some of these events are quite strange (e.g. 'abnormal crying', 'fat disorder', 'vein pain' etc). It would be more useful to give greater detail on the very common adverse events e.g. 'breast symptoms' is very non-specific.

- **Dosage**

It is recommended that additional contraception is used for the first 7 days (even if starting on day 1 of the cycle) when there has been no preceding hormonal contraception. This is not what international guidelines recommend for starting COCs on day 1 of the cycle and it is not clear where this advice has been derived (as so few of the women in the trials were new starters).

### MEDICINE CLASSIFICATION

Prescription only

### OVERALL SUMMARY/DISCUSSION

The first and perhaps most important issue with this application is that of dose selection. From the PK studies a dose of 750mcg EE was selected for the clinical studies, although it appeared from the first study that 600mcg was adequate to maintain target serum levels. The justification for choosing the higher dose is not entirely clear, but may have been to allow for slightly lower absorption from the abdomen.

It is important to note that all the clinical studies were performed with a patch containing 750mcg EE, but the product on which authorisation is sought contains 600mcg EE. This suggests the dose of EE may have been reduced following assessment of this application in other countries, but I can find no reference to this inconsistency in the application submitted to MAAC.

The clinical evidence submitted in this application have demonstrated that EVRA (defined as a 20cm<sup>2</sup> patch containing 6mg 17d-NGM + 0.75mg EE) is an effective contraceptive with an overall Pearl Index of less than 1. The limitations of these trials mean they are likely to over-estimate the efficacy of this product which may be lower in real-life use (and also efficacy may be lower with a lower dose of EE in the patch). EVRA showed similar efficacy to two different COCs - this is perhaps surprising as with the anticipated (and demonstrated) greater compliance with the patch regime, it might be expected to have significantly higher efficacy than oral daily dosing.

The safety data are somewhat concerning. The incidence of systemic effects such as breast symptoms and nausea was double that of the COCs in both trials, which perhaps suggests that serum levels of steroid hormones are too high following transdermal administration. The higher incidence of systemic reactions and the relatively high incidence of application site reactions (around one third women) are reflected in the higher discontinuation rates for women using EVRA compared to those using COCs.

A particular concern is the high incidence of VTE in the women using EVRA in the pivotal studies. Whilst there were other contributing factors for some of the women (surgery, immobilisation etc) and some doubt over confirmation of thrombosis in others, these factors will also be present in real life use. Even if some of the cases are excluded, the incidence of VTE is higher than that reported for third generation COCs. This may again be due to higher serum levels of EE after transdermal administration.

There are no efficacy or safety data beyond one year of use for this product, which may be used for several years (perhaps even 10 years or more?) by some women. The long term risks are therefore unknown, but given the observed effects in the clinical trials the risk of VTE and/or breast problems may prove to be too great for long term use.

It must be questioned whether this product offers any advantages over the oral contraceptive pill. For some women who can't remember to take pills, there may be some benefits, but they must still remember to change the patch weekly (would this be more or less difficult to remember?). Overall, efficacy was the same as COCs and the side effects and safety concerns were greater (and the long-term effects are unknown). Thus for women who are suitable for combined hormonal contraception there seems to be little to recommend it over the Pill.

#### OUTSTANDING ISSUES

I would not recommend authorisation of this product until the following issues are resolved:

1. Why is the dose of EE in the proposed patch (600mcg) lower than that in the product used in the pivotal clinical trials (750mcg)?
2. Are there any clinical trials (providing efficacy and safety data) for a patch containing 600mcg EE (other than the small preliminary PK study which used this dose)?
3. Is the high incidence of thrombo-embolic disorders acceptable?
4. Should longer-term data be requested?