

## Evra

Concise evaluated information to support the managed entry of new medicines in the NHS

### Summary

Evra™ was launched in May 2003 as the first combined contraceptive patch. Evra™ delivers 150mcg of norelgestromin and 20mcg of ethinylloestradiol per 24 hours and should be applied weekly for three weeks, followed by a patch-free week. Pharmacokinetic studies have shown that ovulation is suppressed if the patch is applied on a variety of sites, such as abdomen, buttocks, upper arm or torso.

Three comparative trials have not shown Evra™ to be more efficacious than combined oral contraceptives (COCs), although one trial is only available in abstract form.

Once weekly application could potentially increase compliance compared to taking a daily oral contraceptive and may be suitable for women who have compliance problems with the oral contraceptive. Evra™ is much more expensive than available COCs.

The incidence of venous thromboembolism (VTE) is as yet unknown with Evra™ and therefore it should be used with caution until this risk is assessed. Second and third generation oral contraceptives may be preferable as the risk is known with their use.

### Introduction

Evra™ is a new three layer 20cm<sup>2</sup> transdermal contraceptive patch containing 6mg norelgestromin and 0.75mg ethinylloestradiol (releasing 150mcg and 20mcg per day respectively). One patch is applied on a different site each week for three weeks, followed by a patch-free week. Ovulation can be suppressed if the patch is applied to the abdomen, buttocks, upper arm or torso. The patch should not be applied directly to the breasts.

### Evidence

Evra™ has been assessed in one open label<sup>1</sup> and two comparative studies.<sup>2,3</sup>

1672 women aged 18-45 years were enrolled into an open label study.<sup>1</sup> The sample size was chosen to provide at least 10,000 cycles (850 women years). 501 women were enrolled for 13 cycles; the rest for six cycles. Five pregnancies due to method failure and one due to user failure occurred. Four of the pregnancies occurred in women over 90kg weight. It has been suggested that women over 70.5kg weight may be at risk of failure of combined oral contraceptives (COCs). The Pearl Index (number of pregnancies per 100 women years) was 0.71 overall (0.59 corrected for method failure). Approximately 90% of women complied with patch wearing. Compliance was determined by checking diary cards, not returned medication. 1.9% of patches became detached and had to be replaced. Adverse reactions were consistent with those seen with COC use.

**Brand Name, (Manufacturer):** Evra™ (Janssen Cilag Ltd)

**BNF Therapeutic Class:** Contraceptive (7.3)

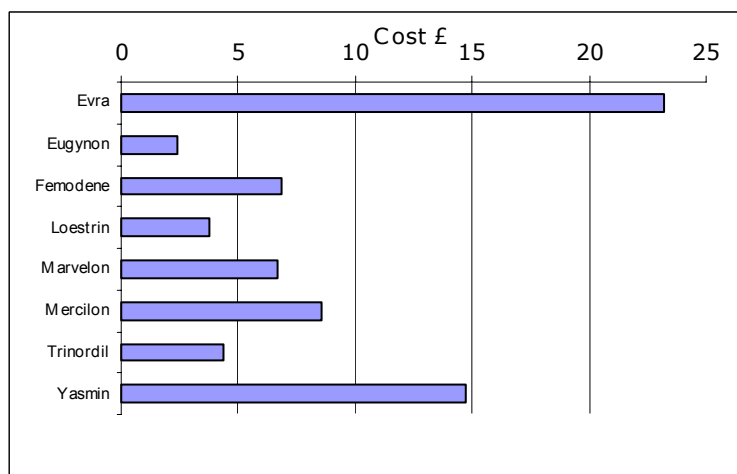
**Licensed Indications:** Female contraception

**Dosage and Administration:** One new patch applied on day 1 (first day of menses), 8 and 15 of the cycle, with a patch free week starting from day 22.

**Marketed:** May 2003.

**Cost Comparisons:**

Cost for 3 months treatment (prices from MIMS June 2003).



Evra™ was compared to Triphasil (an oral triphasic COC, equivalent to Logynon and Trinordil in the UK), in 1417 women aged 18-45 years (812 Evra™, 605 Triphasil); in a randomised, open label study.<sup>2</sup> The study size was chosen to provide 400 person years of observation for the patch. One third of subjects were enrolled for 13 cycles; the rest for six cycles. Analysis was by modified intention to treat. The primary outcome was contraceptive efficacy. Four method failure pregnancies occurred in each group. Overall, five pregnancies occurred in the patch group and seven in the COC group. There was no significant difference in overall Pearl Index (Evra™ 1.24; Triphasil 2.18) or in cycle control from cycle 3. Overall compliance, as determined by diary entries, was better with Evra™ (88.7%) compared to Triphasil (79.2%). The contraceptive efficacy was comparable to that of Triphasil although the sample size was small.

Evra™ was compared to Mercilon in 656 women in a randomised open label study, available only in abstract form.<sup>3</sup> One third of subjects were treated for 13 cycles; the rest for six cycles. Four subjects using Evra™ and two using Mercilon fell pregnant. The overall and method failure Pearl Indices were 0.88 and 0.66 for Evra™ and 0.56 and 0.28 for Mercilon. Life table analysis indicated that the overall probability of pregnancy through 13 cycles was 0.5% for Evra™ and 0.3% for Mercilon (p not significant). Perfect compliance was 94.4% in the Evra™ group and 87.8% in the Mercilon group.

EMA guidelines recommend that a study of a new contraceptive should be large enough to give an overall Pearl Index with a 95% confidence interval not exceeding 1. This may require 20,000

cycles. In the licensing assessment for Evra™, data from the above three trials were pooled giving information on 22,160 on-therapy cycles in 3,319 women, with 613 women completing treatment for 13 cycles. The overall Pearl Index was 0.88 [95% CI 0.43 to 1.32] and that for method failure, 0.7 [0.31 to 1.10]. The probability of pregnancy was 0.8% through 13 cycles. This meets the EMA requirements for contraceptive efficacy and Evra™ was judged to be as efficacious as COCs.

## Safety

In trials adverse effects, apart from application site reactions, were typical of oral contraceptives and occurred with similar frequency. The Summary of Product Characteristics states that there is no evidence that a contraceptive patch is any safer than a COC. The risk of VTE associated with the use of Evra™ is as yet unknown.

## Place in Therapy

Evra™ provides contraceptive efficacy and cycle control comparable to that of COCs. Trials suggest that it is associated with a higher rate of compliance. However, Evra™ is a much more expensive contraceptive than any of the COCs currently available, and the risk of VTE is unknown. It is possible that Evra™ may be of use in women who are continuously non-compliant with COCs and in whom pregnancy is undesirable.

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The full London New Drugs Group review can be seen on [www.druginfozone.nhs.uk](http://www.druginfozone.nhs.uk) (Password required).

## Key Papers

1. Smallwood GH, Meador ML, Lenihan JP, Shangold GA, Fisher AC, Creasy GW. Efficacy and safety of a transdermal contraceptive system. *Obstet Gynecol* 2001; 98: 799-805.
2. Audet MC, Moreau M, Koltun WD, Waldbaum AS, Shangold G, Fisher AC et al. Evaluation of contraceptive efficacy and cycle control of a transdermal contraceptive patch vs an oral contraceptive. *JAMA* 2001; 285: 2347-2354.
3. Hedon B, Helmerhorst FM, Cronje HS, Shangold G, Fisher A, Creasy G. Comparison of efficacy, cycle control, compliance and safety in users of a contraceptive patch vs an oral contraceptive. *Int J Gynecol Obstet* 2000; 70 (S1): S78. Abstract only.

## Risk management issues:

In February 2002 the CPMP voiced concerns regarding the residual amount of hormones that may be left on the patch after use. If the patch is not properly disposed of, these hormones may reach the aquatic environment and have subsequent adverse effects. Janssen-Cilag at the time stated they would include a disposal container with the patch. Once the Evra patch has been used, it should be resealed in its original pouch and disposed of in a bin.

The patch should be applied to the abdomen, buttocks, upper arm or torso. A different site should be used each time. If a patch is detached a new one should be applied.

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