

## New Product Review (September 2003)

### Norelgestromin/ethinyl oestradiol transdermal contraceptive system (Evra®)

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This new transdermal contraceptive system (contraceptive patch), Evra® (Janssen-Cilag), received a UK product licence in 2003.

In clinical trials:

- Consistent doses of norelgestromin and ethinyl oestradiol are released into the systemic circulation daily. Pharmacokinetic data suggest that levels are sufficient to inhibit ovulation for at least 7 days.
- The overall Pearl index for the contraceptive patch (1.24; 95% CI 0.19–2.33) was similar to that of a triphasic combined oral contraceptive (COC) pill (2.18; 95% CI 0.57–3.8).
- Self-reported 'perfect' compliance was significantly better with the contraceptive patch (88.2%) than with a combined contraceptive pill (77.7%).
- Patch detachment, requiring replacement with a new patch, with normal daily activity is uncommon (4.6%).
- Breakthrough bleeding and spotting were significantly more common with the contraceptive patch than with combined oral contraception in the first two cycles but differences were not significant by cycle three.
- In general, reported side effects were not significantly different with contraceptive patch or combined pill use. However, breast tenderness in the first two treatment cycles was more common with patch use. Symptoms were mild to moderate in 85% of women and were rarely treatment limiting.
- Currently, there are limited data regarding risk of venous thromboembolism, and cervical or breast cancer with the contraceptive patch.
- No clinically significant alterations in metabolic or haemostatic parameters were identified with contraceptive patch use.

A month's supply of the contraceptive patch costs £7.74. Combined oral contraception prices range from approximately £0.80 to £5.00 and hormone replacement therapy patches range from £10.00 to £13.00.

The contraceptive patch offers additional choice for women who wish to use a combined hormonal method of contraception.

#### Background

Inevitably there are limited long-term safety data for any new contraceptive method, in particular regarding venous thromboembolism and breast or cervical cancer risk. Detailed scientific studies, performed in a small number of women, provide evidence on mode of action. Larger clinical trials examine efficacy, side effects and acceptability. The number of woman-years of exposure is less than for established methods and all available evidence should be considered before prescribing new products. However, many existing products have been licensed for many years and may not have been the subject of recent evidence-based assessments.

#### What is the transdermal contraceptive system?

Each 20 cm<sup>2</sup> patch delivers 150 µg (micrograms) of norelgestromin (17-deacetyl norgestimate) and 20 µg ethinyl oestradiol (EE) daily into the systemic circulation.<sup>1</sup> Constant serum levels of EE and norelgestromin were observed in an open-label, randomised study over three cycles.<sup>2</sup> Norelgestromin is the primary active metabolite of norgestimate,<sup>1</sup> which itself has been administered orally with EE providing safe effective contraception.<sup>3</sup>

#### How does the contraceptive patch work?

An open-label, randomised, parallel group trial was conducted to investigate the dose of a contraceptive patch

which would inhibit ovulation.<sup>4</sup> A total of 610 women of reproductive age were recruited and randomised to receive a 10, 15 or 20 cm<sup>2</sup> contraceptive patch or a combined oral contraceptive (COC). Serum progesterone levels were measured on Days 7, 14, 21 and 28 of cycles one, three and seven. A progesterone level <1 ng/mL was considered evidence of anovulation. Ultrasound scan was used to assess follicular growth in a subset of 25 women in each group together with a measurement of serum luteinising hormone and oestradiol. In cycles one and three, 88.4% of women (114) using a 20 cm<sup>2</sup> contraceptive patch had progesterone levels <1 ng/mL and were deemed anovulatory. Anovulation was also seen in 88.4% of COC users.

#### How should the contraceptive patch be used?

The contraceptive patch comprises three layers – a protective outer layer, a medicated adhesive layer and a clear liner, which is removed prior to application. An open-label, randomised, crossover study identified that the absorption of norelgestromin and EE was similar when the contraceptive patch was applied to the upper outer arm, upper torso (excluding breast), buttock or lower abdomen.<sup>5</sup> The Summary of Product Characteristics (SPC) recommends that a single patch be applied on the first day of menstruation to one of these four areas. This patch should be removed and replaced

with a new patch on the same day of the following week.<sup>6</sup> A new patch is applied weekly for three consecutive weeks. The fourth week is patch-free, allowing a withdrawal bleed. A new patch is then applied after seven patch-free days.

Pharmacokinetic data suggest there is sufficient absorption of norelgestromin and EE to maintain serum levels within the reference range for up to 10 days.<sup>7</sup> Women do not therefore need to reapply a new patch at exactly the same time every week. If women forget to remove the patch on Day 7, evidence suggests that contraceptive protection is provided for a further 2 days. If the patch remains applied for more than 9 days, contraceptive protection is assumed lost. If women wish to delay menses, the patch-free week can be delayed. However, after six consecutive patches have been used, the SPC recommends there should be a patch-free week.<sup>6</sup>

The patch should be pressed down firmly onto the skin to ensure adhesion. In a randomised, comparative trial,<sup>8</sup> patch detachment, requiring replacement of a new patch, was uncommon (4.6%). Complete detachment occurred in 1.8% of women and partial detachment in 2.8%. In an open-label, randomised study, 30 women were recruited to use the patch on the abdomen for 7 days under one of six conditions (i.e. normal activity, sauna, whirlpool, treadmill, cool water immersion, or a combination of activities). Serum concentrations of norelgestromin were consistent throughout the study, and although levels of EE fluctuated this was not clinically significant.<sup>9</sup>

### How effective is the contraceptive patch?

#### Efficacy

Contraceptive efficacy was investigated in a comparative study in which women were randomised to a triphasic levonorgestrel-containing COC (n = 856) or to the contraceptive patch (n = 639).<sup>8</sup> The overall Pearl index for the contraceptive patch was 1.24 per 100 woman-years (95% CI 0.19–2.33) and for the COC was 2.18 (95% CI 0.57–3.8). When method failure was considered, the Pearl index for the contraceptive patch was 0.99 (95% CI 0.02–1.96) and for the COC was 1.25 (95% CI 0.02–2.47). An open-label, non-randomised, single-arm, multicentre trial investigated women using the contraceptive patch over six cycles (1171 women) or 13 cycles (501 women).<sup>10</sup> Of the 1672 women who started the contraceptive patch, 72% completed the study. Of the six pregnancies that occurred in this study, four were in women weighing >90 kg. The SPC suggests that the contraceptive patch is less effective in women weighing ≥90 kg.<sup>6</sup>

#### Compliance

Compliance with the contraceptive patch compared with COC was investigated in an open-label, randomised, controlled trial.<sup>8</sup> Similar results for patch compliance were found in an open-label, non-randomised, single-arm, multicentre trial.<sup>10</sup> Compliance was defined as 'perfect' when women applied a patch, or took COC, consistently for 21 days, followed by a 7-day patch-free (or placebo-taking week). Women completed diary cards and recorded patch replacement information. These diary cards were used to assess compliance and patch detachment due to reasons other than routine replacement. Using this subjective measure of compliance in well-motivated study patients, 'perfect' use was reported for 88.2% of women using patches and for 77.7% of women using COC. However, this improved compliance did not have a significant effect on reducing failures rates.

### What are the contraindications to the contraceptive patch?

The World Health Organization *Medical Eligibility Criteria for Contraceptive Use* for combined oral contraception suggests circumstances for COC use where risks outweigh benefits.<sup>11</sup> It is likely that the contraceptive patch will have contraindications similar to COCs. No data are available on the use of the contraceptive patch by women using liver enzyme-inducers. The SPC for the contraceptive patch suggests that barrier contraception should be used in addition to contraceptive patches when liver enzyme-inducing drugs are used; or that an alternative method should be considered. Although first-pass metabolism in the liver is avoided with transdermal administration of hormones, the data on contraceptive efficacy with concurrent antibiotics are limited. An open-label, randomised, crossover study investigated the hypothesis that the co-administration of tetracycline and the contraceptive patch would have no effect on the pharmacokinetics of norelgestromin and EE.<sup>12</sup> Oral tetracycline 500 mg was administered four times daily for 3 days before, and 7 days after, applying a patch. No significant effect on the pharmacokinetics of norelgestromin or EE was identified. The SPC advises use of barrier contraception when using antibiotics (with the exception of tetracycline) and for 7 days after their discontinuation.<sup>6</sup>

### What are the side effects of the contraceptive patch?

#### Discontinuation rates

A randomised trial suggested a high rate of discontinuation with both the contraceptive patch and COCs.<sup>8</sup> A total of 241/812 women who received the patch withdrew from the study (29.7%) and 147/605 women who received the COC withdrew (24.3%). Two-thirds of women recruited to either arm of the study were assigned to receive treatment for only 6 months and one-third for 13 months. A total of 55% of study participants had switched from an oral contraceptive method immediately before being recruited into the study. The data reported do not allow an assessment of the time to discontinuation of either treatment and rates may appear high because most women were using the treatment for a maximum of 6 months.

Commonly reported side effects associated with the contraceptive patch included: headache (21.9%), nausea (20.4%), site reactions (20.2%) and breast tenderness (18.7%).<sup>8</sup> In a trial, breast discomfort with COC use (5.8%) was significantly less common than with the contraceptive patch. The increase in breast tenderness seen in patch users compared to COC users was only significant in cycles one and two (15.4% compared to 3.5% in cycle one and 6.6% compared to 1.5% in cycle two).<sup>8</sup> Most of the women (85%) who described breast tenderness had only mild-to-moderate discomfort and the symptom led to discontinuation in only 1.0% of patch users. Site reactions were seen with contraceptive patch use in 20.2% of women but led to discontinuation in only 2.6% of women.<sup>8</sup> The mean alteration in body weight during the trial was an increase of 0.4 kg for both patch and pill users.

#### Disruption of bleeding pattern

Breakthrough bleeding (BTB) and spotting with the contraceptive patch appeared similar to that for a triphasic COC in a randomised, comparative trial.<sup>8</sup> BTB and spotting were more common in cycles one and two with patch use than with COC use. In cycle one, BTB and spotting were reported by 18.3% of patch users compared to 11.4% of COC users. In cycle three, 10.0% of patch users reported BTB compared to 8.8% of COC users. An open-label, non-randomised trial identified good cycle

**Table 1** Approximate net price of the contraceptive patch compared to British National Formulary prices for a selection of combined oral contraceptives (COCs) and combined hormone replacement therapy (HRT) patches per month of use<sup>13</sup>

Contraceptive method	Net price per month of use
Contraceptive patch Evra®	£7.75
Monophasic COCs	
Ovranette®	£0.80
Eugynon 30®	£0.80
Microgynon 30®	£0.85
Loestrin 20®	£0.85
Loestrin 30®	£1.30
Cilest®	£2.15
Marvelon®	£2.20
Minulet®	£2.30
Femodene®	£2.30
Femodette®	£2.75
Mercilon®	£2.85
Yasmin®	£4.90
Combined oestrogen and progestogen HRT patches	
Estracombi®	£11.15
Femseven Conti®	£12.90
Femseven Sequi®	£10.00

control in 1164 women recruited to use the contraceptive patch.<sup>10</sup> BTB and spotting were reported by 17.5% of women in cycle one, falling to 9.2% by cycle 13.

#### Metabolic effects

A pulmonary embolism occurred in one contraceptive patch user,<sup>10</sup> but the patch had been used up until the time of major surgery. No clinically significant alterations in laboratory parameters have been identified with contraceptive patch use.

#### Is the transdermal contraceptive patch cost-effective?

Currently, there are insufficient published data to assess cost-effectiveness of the contraceptive patch compared to other methods of contraception. Economic modelling data from the manufacturers suggest that improved compliance and reduced rates of unintended pregnancy with the patch provide cost savings overall. Approximate net monthly prices from the *British National Formulary*<sup>13</sup> are included for information in Table 1. Many existing contraceptive products have been licensed for many years, which is reflected in their lower price. Contraceptive patches compare favourably in price to other transdermal delivery systems, such as HRT.

#### What does this new contraceptive patch add to contraceptive choice for women?

The COC is the most commonly used method of contraception in women aged 16–49 years.<sup>14</sup> It is unlikely that all COC users would consider using a

contraceptive patch. The efficacy of oral hormonal contraception varies with typical and perfect use. In a retrospective, population study, 23% of COC users admitted to missing one or more pills in the previous cycle.<sup>15</sup> Self-reported compliance with the contraceptive patch appeared better than with a COC. A Cochrane systematic review compared efficacy, cycle control, compliance and safety for the contraceptive patch and for combined oral contraception.<sup>16</sup> The review concluded that self-reported compliance was better with the patch but, overall, the efficacy data are similar for both methods. This new transdermal contraceptive patch provides a new delivery system and another contraceptive choice for women.

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The Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit (CEU) team has prepared the advice given in this New Product Review. It is based on a structured search and review of published evidence available at the date of preparation. The advice given here should be considered as guidance only. Adherence to it will not ensure a successful outcome in every case and it may not include all acceptable methods of care aimed at the same results. This response has been prepared as a service to FFPRHC members, but is not an official Faculty Guidance product; a different and lengthier process produces Faculty Guidance. It is not intended to be construed or to serve as a standard of medical care. Such standards are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances. Members are welcome to reproduce this document by photocopying or other means, in order to share the information with colleagues.

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