

## SCIENTIFIC DISCUSSION

**This module reflects the initial scientific discussion for the approval of Evra. This scientific discussion has been updated until 1 October 2003. For information on changes after this date please refer to module 8B.**

### 1. Introduction

EVRA is a contraceptive patch of 20 cm<sup>2</sup> for transdermal administration that contains 0.75 mg of ethinyl estradiol (EE) combined with 6 mg of norelgestromin (NGMN) as active substances. Subsequently, in February 2003, the European Commission authorised a change to a new manufacturing site. In order to achieve bioequivalence between the two patches, the content of EE was reduced to 0.6 mg per patch. The content of NGMN remained unchanged.

Ethinyl estradiol has been used extensively as the estrogenic component of many oral contraceptives. By contrast NGMN is a new progestagenic component. NGMN is, however, the primary active metabolite of norgestimate (NGM), which is the progestagenic component of several combined oral contraceptives already authorised. *In vivo*, the deacetylation of NGM occurs predominately during the oral absorption process, as a first-pass effect. NGMN was chosen as the progestagenic component of the patch as it has been shown to pass through the skin.

EVRA is the first combined contraceptive for transdermal application designed to deliver effective levels of the two hormones during the 7-day period of wear. The formulation is claimed to deliver approximately 150 microgram NGMN and 20 microgram EE to the systemic circulation per day during each day of wear. The development of EVRA is based on the rationale that a patch has a greater acceptability and ease of compliance, and that the dose delivery by the transdermal route is unaffected by gastrointestinal disturbances.

The approved indication is “for female contraception. EVRA is intended for women of fertile age. The safety and efficacy has been established in women aged 18 to 45 years”.

The dose recommendation includes the use of one patch per week (7 days) for three consecutive weeks, to be followed by one patch-free week.

### 2. Chemical, pharmaceutical and biological aspects

#### Composition

EVRA is a transdermal patch (matrix type), which contains 6 mg of NGMN and 0.75 mg of EE as active substances per patch. The patch delivers approximately 150 µg NGMN and 20 µg EE per day. The patch is a thin flexible square with rounded corners. The surface in contact with the skin is 20 cm<sup>2</sup>. Three different layers are distinguishable: a non removable polyester protective film (backing layer), the adhesive matrix containing the active substances with a non woven polyester fabric as a structural support, and a clear transparent polyester removable protective layer (release liner).

Other ingredients include polyisobutylene/polybutene, lauryl lactate, crospovidone, and non-woven polyester fabric. The rationale for the selection of the individual excipients is also given.

There are no components from animal origin entering in the composition of the finished product.

Each patch is packed in an opaque, white heat-sealed pouch. The pouch has a laminated construction of bleached machine glazed paper, low density polyethylene, aluminium foil (9 µm) and inner low density polyethylene heat-seal layer. A supply of one cycle consists of three pouches packed in a cardboard carton.

## **Active substances**

### **Ethinyl estradiol (EE)**

EE complies with the Ph. Eur. A certification of Suitability of the Monograph of the European Pharmacopoeia is available for the manufacturer.

Results of 10 batches manufactured are provided. All batches conform to specifications.

The stability of ethinyl estradiol has been investigated under stressed conditions. The degradation chemistry was studied in solution and in the solid state. Aged active substance did not contain significant amount of degradation products. Also, long-term stability data are presented, up to 48 months (4 batches; 25°C/60 % RH). Parameters studied are acceptable (including methods used). The results show that the substance is very stable and extreme conditions were required to cause degradation. Therefore, on this basis the proposed re-test period of 12 months is acceptable.

### **Norelgestromin (NGMN)**

Information on NGMN has been supplied in the form of an EDMF.

NGMN is (17 $\alpha$ )-13-ethyl-17-hydroxy-18, 19-dinorpregn-4-en-20-yn-3-one-oxime. It is the primary active metabolite of norgestimate (NGM).

NGMN has two types of isomerism:

- Optical isomers due to asymmetry of the molecule (6 asymmetric carbon atoms). The particular optical isomer is guaranteed by the appropriate starting material and by the synthetic route.
- Geometrical isomerism, NGMN is a mixture of anti- (E) and syn- (Z) isomers.

Crystalline and amorphous forms have been found. These characteristics however are not relevant for this application because the substance is dissolved in the final product.

NGMN is manufactured by the hydrolysis of the 17-acetyl functional group of NGM (deacetylation). The starting material NGM is a well known progestagenic compound used in oral contraceptive medicinal product authorised in the EU, the control and synthesis are well described and validated.

NGMN specifications include tests for identity (IR, HPLC, Specific Optical Rotation), assay (HPLC, 98-102 %) and a number of purity tests such as tests for related substances, residual solvents (GC, acetone, cyclohexane, isopropyl ether, ethanol, methanol), heavy metals.

Characterisation of each impurity is provided; the major impurities are NGM and norgestrel (NG). The impurities limits in the specification are justified by toxicology studies.

Batch analytical data are presented in four batches used for the manufacture of clinical supplies and one batch used in toxicological studies and also for 8 batches (production size), all indicating compliance with the specification and good uniformity and control of the synthetic process. All control methods have been adequately validated.

Stability studies for NGMN have been performed by the active substance manufacturer and by the applicant. The stability batches were stored in double polyethylene bags in cardboard boxes. Methods are validated and stability indicating. They included assay, appearance, water content, ratio of anti-syn isomers, and degradation products (HPLC).

This data provided is sufficient to confirm the proposed re-test period, 3 years.

## **Other ingredients**

Crospovidone is described in the Ph. Eur and the USP/NF. It is controlled according to the Ph Eur.

Internal monographs are proposed for the rest of the excipients, which are not described in a Pharmacopoeia, e.g the adhesive and the polyester fabric. Lauryl lactate is a novel excipient in

pharmaceutical use, however a substantial amount of information exists in relation to its use in cosmetics.

Analytical certificates of the packaging materials from the suppliers have been submitted.

### **Product development and finished product**

The conversion of NGM to NGMN was not expected to occur extensively when NGM was administered transdermally. In addition NGMN would be more effective in skin penetration than NGM and was chosen chiefly on this basis. Acceptable transdermal delivery was investigated at different sites: abdomen, buttock, upper outer arm and upper torso with satisfactory results.

The aim was to develop a patch, which achieves plasma levels similar to those obtained after an oral administration of EE and NGM. The capacity of both substances to permeate through the skin was demonstrated during the pharmacokinetic studies, where it was shown that the serum levels in women using EVRA achieved similar plasma levels as 250 µg NGM + 35 µg administered orally.

In the pharmaceutical development, *in vitro* flux rate studies with human cadaver skin were used as a development tool for evaluating prototype performance.

Three classes of pressure sensitive adhesive, with different solubility parameters were also investigated in order to have a system that could provide 7-day wear and delivery of the two active substances.

The batches used in clinical trials are the same as those intended for marketing.

The manufacturing process is established in accordance with Good Manufacturing Practices and with internal standard procedures. The finish product is manufactured in 4 steps: (1) mixture of ingredients, (2) coating, drying and lamination, (3) control of the final laminate, and (4) die cutting of the patches and primary packaging.

The manufacturing process has been validated by a number of studies for the four major steps of the manufacturing process in three industrial batches, for instance mixing apparatus, purity of lauryl lactate, mixing optimisation, optimisation of coating parameters.

### *Product Specification*

The product specifications include tests by validated methods for appearance, identification of active substances (HPLC and TLC), assay (HPLC, NGMN and EE), lauryl lactate (GC), content uniformity (Ph. Eur.), dissolution, peel force, adhesive strength, and microbial purity. Degradation products are detected by HPLC. GC detects residual solvents and a limit is defined for each of the solvents.

Degradation products are controlled and their limits are justified by reference to stability studies and toxicology studies.

### **Stability of the Product**

The stability of the EVRA patches has been studied on three industrial size batches. The patches were stored according to the conditions described by ICH for 24 months at 25°C/60 % RH, for 12 months at 30°C/60 % RH, and for 6 months in accelerated conditions 40°C/75 % RH. Additional stress conditions were studied: 1000-foot candles on unpouched patches and pouched patches during 3 to 7 days.

The parameters tested were appearance, assay active substances, degradation products, microbial purity, ratio of lauryl alcohol and lauryl lactoyl lactate, ratio NGMN anti to NGMN syn, peel/adhesive strength and dissolution.

Results have been generated by validated, stability indicating methods and indicate satisfactory stability. These results support the shelf life stated in the Summary of Product Characteristics.

### 3. Toxicopharmacological aspects

Since EE has already been extensively used for many years as the estrogenic component of many approved oral contraceptives in Europe, the preclinical profile of EE has been well documented in published literature. No new studies using EE have therefore been performed. The preclinical profile of EE alone will not be discussed in this document unless relevant for the combination.

Norelgestromin (NGMN) is a new progestogenic component. It is, however, the primary active metabolite (17-deacetylnorgestimate) of norgestimate (NGM), which is the progestagenic component contained in oral contraceptives already authorised in Europe. *In vivo* the deacetylation of NGM occurs predominantly during the oral absorption process, as a first pass effect. Preclinical data have been previously generated using oral/parenteral administration of NGM and/or NGMN to support the oral use of NGM as progestin of oral contraceptives.

The preclinical development of EVRA was therefore based on a bridging strategy. The pharmacological/toxicological data, which were previously obtained with NGM have been used to support the topical use of NGMN. Additional studies have only been carried out when necessary.

This bridging strategy was considered acceptable since preclinical pharmacokinetic studies have shown that after administration of NGM, systemic exposure to NGMN was far higher than that of the parent compound or other metabolites due to first pass metabolism. As a consequence, it is impossible to evaluate the pharmacological profile of NGM alone and data obtained after administration of NGM can all be considered to support the activities of NGM/NGMN and/or NGMN alone.

#### **Pharmacodynamics**

As above-mentioned, data obtained after administration of NGM can all be considered to support the activities of NGM/NGMN and/or NGMN alone. This consideration was supported by three studies, which showed similar progestagenic and androgenic activities between NGM/NGMN and NGMN alone.

All the pharmacodynamic studies on NGM/NGMN, except one, had already been reviewed during the approval procedure of oral contraceptives containing NGM. From this initial evaluation it was concluded that NGM/NGMN could be considered as an efficacious and safe progestagenic component. Since in almost all preclinical studies NGMN acted as the primary progestagenic component, the conclusions made on the use of NGMN alone as progestagenic component of EVRA could be extrapolated from the use of the already approved medicinal products.

#### **Mechanism of action**

##### *Anti-ovulatory activity*

The ability of NGM/NGMN to inhibit ovulation at different dose levels was measured in a number of species and compared to that of other progestogens and in combination with EE. NGMN and NGM were equally potent *in vivo* in inhibiting ovulation and the combined effects of NGM/NGMN and EE on ovulation in rats after oral administration were, at most, additive, and were only seen at relatively high doses. The estrogenic component EE is added mainly to provide menstrual cycle control.

##### *Other activities*

Both NGM and EE have further pharmacological activities, which are indirectly related to the proposed indication and are due to the sex hormonal activities of these steroids. These are summarised below.

NGM seems to have a moderate progestagenic activity based on its effects on endometrial proliferation in rabbits, maintenance of pregnancy in rats and binding to the progestogen receptor *in vitro*. In the same way EE exerts its estrogenicity by binding to estrogenic receptors and stimulating cell growth in various tissues.

NGM/NGMN seemed less androgenic than levonorgestrel (LNG) as assessed by its ability to stimulate ventral prostate growth and its effects on sex hormone binding globulin (SHBG).

Effects on early gestation were studied in rats, New Zealand White rabbits and Hartley guinea pigs. NGM, administered orally at about 5-10 mg/kg (rats), 15 mg/kg (rabbits) and 10 – 30 mg/kg (guinea pigs) inhibited pregnancy up to 100 % in some cases but NGM + EE was more effective than NGM due to its EE component. Even if no such effects would be expected in women at the clinical dose, it is adequately stated in the Summary of Product Characteristics that pregnancy should be ruled out before treatment initiation.

NGM administered orally to female Wistar rats produced a significant reduction in adrenal gland weights at the highest dose (0.5 kg/mg) but there was no remarkable alteration in hormone concentrations and the only histological change observed was a mild uterine stimulation. The relative biological activity of isomers of norelgestromin has been demonstrated.

#### General and safety pharmacology programme

NGM did not have any significant effect on the central nervous system of rats when administered orally at doses up to 25 mg/kg nor on the autonomous nervous and cardiovascular system of dogs when given intravenously at doses 0.5 mg/kg.

#### Pharmacokinetics

A number of pharmacokinetic studies and publications from literature were provided to describe the pharmacokinetic profile of EE, NGM and NGMN. Most of the studies were already evaluated in the context of the applications for orally administered NGM. The preclinical development of oral NGM is of older date and in these experiments radiolabelled test compounds were used. Consequently, metabolites in serum were not quantified. Therefore, bridging studies were performed to determine serum concentrations of NGM, NGMN, and the metabolites after oral administration of NGM with or without EE, using LC/MS techniques. These studies were performed in rats, rabbits and rhesus monkeys to investigate the exposure that was likely to have been achieved in the main oral toxicity studies with NGM. No studies have been performed in mice and dogs since these species are not directly relevant for the safety evaluation.

New *in vitro* studies have been performed with NGMN to support this application: protein binding, interaction with P-450 enzymes, metabolism in rat hepatic S9 fraction and toxicokinetic data were obtained from toxicological studies.

#### **Absorption**

The pivotal study in rats measured the serum concentrations of NGM and its metabolites, after the first and final doses of a 14 day oral study with NGM + EE in non-fasted females (0.3/0.06 mg/kg; 0.6/0.12 mg/kg and 3.0/0.6 mg/kg NMG/EE, respectively). At all three doses NGMN was the major analyte on both study days. By contrast, NGM and 3-keto NGM (the metabolite of NGM) were only quantifiable at the highest dose.

A study with NGM alone, in both male and female Sprague-Dawley rats confirmed the same relative exposure to the compound and primary metabolites at the high oral doses (up to 100 mg/kg/day).

The main Rhesus monkey study investigated serum concentrations of NGM and its metabolites following single and repeated dosing of NGM+EE. The dose levels of NGM and EE were equivalent to the low and high doses used in the last six years of the long-term (10-year) monkey toxicology study (5 µg/kg NGM + 0.7 µg/kg EE and 250 µg/kg NGM + 35 µg/kg EE). The results confirmed a dose-related exposure to NGMN, with essentially no change in the concentrations during repeated administration. By contrast, NGM was only detected in a few of the samples from the high dose group, and 3-keto NGM was not detected in any of the samples from either dose group.

When NGM + EE (300 µg/kg NGM + 60 µg/kg EE) was administered orally to female rabbits, neither NGM nor NGMN were detected in the serum. This suggests a marked first pass effect in the rabbit not only for the parent compound but also for its primary active metabolite. Subcutaneous dosing of pregnant rabbits with NGMN from Days 7 to 19 of gestation, with or without concomitant exposure to EE showed that concentrations of NGMN were dose related but less than proportional, likely to be due to absorption-rate limited pharmacokinetics.

The serum concentrations of norgestrel (NG), a secondary active metabolite of NGM, which is also the active component of registered combined oral contraceptives, were relatively low in orally dosed rats and subcutaneously dosed rabbits. By contrast, in the 21-day oral NGM study in monkeys the AUC for NG were more than twice those for NGMN, which corresponds with the NG exposure in women.

Following a single application of a patch (6.0 mg NGMN + 0.6 mg EE 20 cm<sup>2</sup> patch) to non-pregnant rabbits for 7 days, maximum serum concentrations occurred between 24 and 72 hours, then declined gradually during the remainder of the application period. This resulted in a lower exposure of NGMN as compared with human exposure achieved with EVRA. Within 24 hours of removing the patch, serum levels of both analytes had fallen below the limit of detection of the assay.

### **Distribution**

Tissue distribution has not been studied after administration of NGMN. However, previous studies were performed with oral doses of radiolabelled NGM. The results indicated extensive distribution of the radioactivity to the skin, muscles, liver, adrenals, and adipose tissue as is seen with other steroid progestogens. Significant retention was not observed.

A specific *in vitro* binding study of NGMN has been performed. Plasma protein binding of NGMN was independent of concentration within the range 0.10 to 100 ng/ml, and was effectively the same in rats, rabbits, rhesus monkeys and women (98.8 to 99.1 %).

### **Metabolism and excretion**

No *in vivo* studies have been performed to profile the metabolites of NGMN. This was acceptable because, apart from any minor products that might be formed directly from NGM/3-keto NGM (a minor metabolite of NGM) the metabolic profile for NGMN is expected to be identical to that of NGM and it is anticipated that the metabolic profile would not be qualitatively different by transdermal and oral routes. Previous studies with NGM showed that metabolism of NGM in rats, dogs, monkeys and humans included hydrolysis of the oxime and acetate moieties; ring A reduction, polyhydroxylation and conjugation. In the dog and Rhesus monkey biotransformation also involved D-homoannulation. From these studies it is concluded that the metabolism of NGM was qualitatively similar in rats, dogs, monkeys and humans.

In rabbits the major metabolic pathway was glucuronidation of NGM and NGMN.

The metabolism of NGMN, NG and EE involves various isoforms of CYP450.

No excretion studies have been performed with NGMN. The results for elimination of the radioactivity of NGM from serum showed comparatively long half-life of 30-50 hours in all species.

### **Interactions**

It was shown on all the species that the co-administration of EE did not markedly modify the disposition of NGM or its metabolites.

## **Toxicology**

Since NGMN has been shown to be the primary metabolite of NGM in human, rat and rhesus monkey, it was considered acceptable to refer to toxicological data generated previously generated with NGM. Since most of the studies included NGM in combination with EE, any toxicological interaction between NGMN and EE was also accounted for.

The bridging strategy was considered acceptable and only new data have been produced with NGMN for reproduction toxicity and mutagenicity. In addition local tolerance studies and a repeated dose dermal toxicity study using EVRA patch have also been conducted. All these new studies have been performed in accordance with the Good Laboratory Practices.

### **Dose extrapolation**

In assessing the exposure margins in the animals with those in humans, systemic exposure systemic exposure to NGMN was observed during toxicity studies. Retrospective oral pharmacokinetic studies to assess systemic exposure to NGMN in oral studies with NGM revealed that AUC values in female rats at the top dose in the pivotal carcinogenicity study with rats was more than 16 times higher than the values in women using NGM 250 µg/EE 35 µg or EVRA. The AUC of NGMN in the 10-year monkey study exceeded that in humans by > 7 fold.

Estimation of safety margins relies mainly on the comparison of exposure rates of norelgestromin in human and in animal studies. The extrapolation of the exposure of NGMN/NG from animal to humans is difficult due to different binding characteristics. While NGMN is exclusively bound by a weak interaction with serum albumin, NG is also avidly bound by SHBG, the extent of which can change during a course of treatment. However it was agreed that this does not compromise the clinical safety of the product. In addition because of the close similarities between NGMN/NG:EE exposures in women using NGM 250 µg/EE 35 µg and EVRA, the established clinical database provides better reassurance than the preclinical.

### **Single dose toxicity**

No acute toxicity studies have been conducted with NGMN. NGM+EE had a very low order of acute toxicity after oral administration. No lethality or toxicity were seen in rats at doses up to 5,000 mg/kg of NMG + EE. It can be assumed that the acute toxicity profile of NGMN will be of the same magnitude.

### **Repeated dose toxicity**

Oral studies with NGM alone or in combination with EE were previously performed in rats, dogs and monkeys. Long-term studies included two oral 24-month studies with NGM+EE in rats, and 2-year and 10-year monkey (Rhesus) studies.

These studies revealed effects most likely related to an exaggerated pharmacological action such as reduction of oestrus cycles, decreased uterine and ovarian weight, decreased serum cholesterol levels and erythrocytes parameters. Assuming that human exposures to NGMN and NG via NGM 250 µg/EE 35 µg and EVRA are similar, these oral toxicity data indicate that EVRA will not pose additional safety issues as compared to this already approved oral contraceptive. It has to be noted that exposure of rats to NG was relatively low. This difference in metabolic patterns between rats and women will not pose a problem, because NG has been used as oral contraceptive for many years and the toxicity of NG was sufficiently studied in monkeys.

In rabbits, topical application of treatment patches (10, 15 or 20 cm<sup>2</sup>) containing up to 6 mg NGMN and 0.75 mg EE (8:1) or placebo patches was made with two new patches applied to shaved sites on each animal per week, giving continuous exposure of 24 hours a day for 28 to 29 days of duration. Clinical observations related to the topical application were limited to irritation at the application site

in all treatment and placebo groups. The erythema was not directly related to the steroid components and was attributed in part to difficulty encountered during patch removal.

Clinical chemistry results indicated statistically significant decreases in serum phosphorus and triglycerides in all treated groups compared to control. Haemoglobin, haematocrit, red blood cells and prothrombin time decreased in all test groups as compared to control. Absolute and relative ovary weight increased in all test groups but there was no microscopic correlate for this difference. The majority of haematological and clinical chemistry changes can be related to an estrogenic effect. Similar changes have been reported in mice, rats, monkeys and dogs. As expected, a number of non dosage-related changes occurred in the reproductive tract. Uterine changes included multifocal decidualization (hypertrophic vacuolated mesenchymal cells) and enlargement with discoloration. These changes are considered physiologic progestagenic and estrogenic effects of the treatment. Thymic lymphoid depletion and deposition of amyloid or amyloid-like material in the spleen were observed in all treatment groups. These effects were not observed in the oral studies. The margins of exposure at the dose levels used in this study compared to the human exposure are small (0.31-0.69 and 0.67-1.13 for NGMN and EE, respectively). These effects seemed however of no concern for humans, based on published data on effects of estrogens and progestogens in rabbits, and the fact that the effects on spleen have not been observed in other animal species, nor are they known from hormonal contraceptive treatment in women. In addition clinical data did not indicate an important difference in exposure to metabolites between the approved oral contraceptive NGM 250 µg/EE 35 µg oral treatment and EVRA.

### **Reproduction studies**

Oral reproduction studies with NGM+EE were previously performed. These included a fertility and general reproductive performance study in rats, two embryo-foetal developmental studies (rats and rabbits), and a perinatal toxicity study in rats.

Dose-related effects on fertility, maternal and foetal parameters, and lactation were observed and are expected responses to the pharmacological actions of these substances. In the embryo-foetal toxicity study, the increase in 'wavy ribs' reported in the high dose group (NGM+ EE (5:1) 300 µg/kg/day) was considered as a skeletal variant rather than a teratogenic response. The change reversed after birth and no teratogenic effects were observed in rabbits after oral administration of NGM + EE.

Because rabbits dosed orally with NGM were exposed to low levels of NGMN, an embryo-foetal toxicity study was performed in this species with subcutaneously administered NGMN with doses ranging from 1 to 6 mg/kg/day. Foetotoxicity, as reduced ossification of the pubis bone was observed at all doses, but the safety margin for this effect is sufficiently high.

The oral reproductive toxicity data indicated therefore that EVRA will not pose additional safety issues as compared to NGM 250 µg/EE 35 µg. Although exposure of rats to NG was relatively low, an additional safety concern is not expected, because NG has been used as oral contraceptive for many years.

### **Genotoxic potential**

Previous *in vitro* and *in vivo* studies conducted with NGM alone and the combination of NGM+EE, and additional *in vitro* and *in vivo* studies conducted with NGMN (Ames test, chromosomal aberration test, CHO/HGPT and micronucleus test) did not indicate any genotoxic potential.

### **Oncogenic/carcinogenic potential**

No carcinogenicity studies have been conducted using NGMN but results from two previously conducted oral carcinogenicity studies in rats and one 10-year oral monkey study, with NGM + EE have been submitted. It is well established that estrogens can cause neoplasms of the mammary glands in rats and therefore the findings in rats regarding mammary neoplasia were considered not to be relevant to women. In the monkey, the neoplasms reported were single occurrence and generally in



different organs. Based on the overall low incidence of neoplasms, the single occurrence of a specific type of neoplasm with known spontaneous occurrence, and in the absence of any of the precursor lesions in any other monkey in the study, the neoplasms were not considered to be treatment related.

### **Local tolerance**

The dermal effects of the 20 cm<sup>2</sup> patch system containing NGMN + EE with the same amounts as in the product intended for marketing were evaluated. The local effects observed in the primary skin irritation study and in the 28-day dermal toxicity study with multiple application of EVRA patches are attributable to the difficulties of patch removal. There was no evidence for contact sensitisation in guinea pigs.

### **Special toxicity studies**

Lauryl lactate is a new excipient to be used for the preparation of medicinal products but has been used in cosmetics. Data have been provided to show that the exposure of lauryl lactate following exposure to EVRA patch would be low. In vivo it is expected to be hydrolysed to lauryl alcohol and lactic acid, which are both endogenous compounds. Single application of lauryl lactate was associated with minimal irritation and no evidence of sensitisation. Preclinical and clinical studies performed with EVRA placebo containing lauryl lactate also showed that the product resulted only in mild irritation and exhibited no potential for phototoxicity and photoallergy. Lauryl lactate was not mutagenic and there was no evidence of systemic toxicity following applications for 28 days in rabbits receiving weekly dermal application of lauryl lactate at the concentration present in EVRA.

These data confirm that the safety of lauryl lactate under the conditions of use is acceptable.

### **Ecotoxicity/Environmental risk assessment**

The CPMP has considered the potential risks and environmental implications of the disposal of EVRA, especially because the patch still contains substantial quantities of EE. Negative effects of low levels (0.1 ng/l) of EE have already been demonstrated not only in the laboratory, but estrogenic effects on fish near sewage treatment works have been found in most investigated countries. These effects include production of egg-yolk proteins in male fish, and the development of fishes with both male and female reproductive tissues, with consequent changes in gender ratio and reduced species reproduction. At higher concentrations (5 ng/l), EE leads to arrest in the development of eggs, i.e. a lethal effect<sup>1</sup>. The finding of EE in both surface water and tap water suggest that EE is transported long distances over long times and is resistant to degradation<sup>2</sup>. Based on the 2001 sales figures of EE in Europe (628.7 kg) and the average volume of wastewater per capita per day (0.20 m<sup>3</sup>, according to Technical Guidance Document in support of Directive 93/67/EEC on risk assessment of new notified substances and regulation (EC) No 1488/94 on risk assessment of existing substances), the estimated predicted environmental concentration surface water (PEC) is 2.28 ng/l. In case the total amount of EE present in EVRA patches is released into aquatic environment the PEC<sub>surface water</sub> will increase to 2.43 2.36 ng/l.

Although these PEC values are below the limit of 10 ng/l for the crude PEC, it was agreed that effective measures should be taken to ensure avoidance of any increase of environmental concentrations of ethinyl estradiol due to market introduction of EVRA. Therefore recommendations on the disposal of the patch were included in the relevant sections of the SPC (sections 4.2 “Posology

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<sup>1</sup> Kime DE and Nash JP. Gamete viability as an indicator of reproductive endocrine disruption in fish. *Sci Total Environ* 1999;233:123-9.

<sup>2</sup> Kuch H.M. and Ballschmiter K. Determination of endocrine-disrupting phenolic compounds and estrogens in surface and drinking water by HRGC-(NCI)-MS in the picogram per liter range. *Environ. Sci. Technol.* 35, 3201-3206, 2001.

and method of administration” and 6.6 “Instructions for use and handling and disposal”), Labelling and Package Leaflet to help protecting the environment.

In addition the applicant agreed to include in the package an appropriate disposal container for used patches prior to marketing the product in the European Union.

In February 2003, the addition of a disposal system to the outside of the container of EVRA was authorised into which the patches should be placed once used. The whole unit can then be discarded with solid waste. The section 6.6 of the SPC, the labelling and the section 3 of the PL were amended with instructions for use on how to dispose of the used patch.

#### 4. Clinical aspects

The clinical development programme of EVRA aimed to investigate the contraceptive safety and efficacy in women. Ten pharmacokinetic and bioavailability studies have been performed; there were five pharmacodynamic studies (including a dose ranging study) and three Phase III studies considered as pivotal for this application (two controlled and one open-label studies); finally, four specialised safety (including dermal safety) and/or secondary efficacy studies, were also submitted.

All the clinical trials were performed according to the Good Clinical Practices and agreed international ethical principles.

EVRA is indicated for female contraception.

#### Clinical pharmacology

##### Pharmacodynamics

The primary mechanism of contraception is inhibition of ovulation. Alterations to the morphology of cervical mucus and to the endometrium also contribute to the efficacy of the product.

Five clinical studies were carried out to evaluate the pharmacodynamic effects of NGMN + EE in terms of ovarian function, endometrial effect and effects on cervical mucus.

In these studies, EVRA was compared with the following combined oral contraceptives (COCs):

| COCS containing as active substances | Doses                                                                                                              |
|--------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| <b>Monophasic</b>                    |                                                                                                                    |
| Norgestimate/EE (NGM/EE)             | 250 µg NGM + 35 µg EE                                                                                              |
| Desogestrel/EE (DSG/EE)              | 150 µg DSG + 20 µg EE                                                                                              |
| Levonorgestrel/EE (LNG/EE)           | 100 µg LNG + 20 µg EE                                                                                              |
| <b>Triphasic</b>                     |                                                                                                                    |
| Levonorgestrel/EE (LNG/EE)           | 50 µg LNG +30 µg EE for days 1-6,<br>75 µg LNG + 40 µg EE for days 7-11,<br>125 µg LNG + 30 µg EE for days 12-21   |
| Norgestimate/EE (NGM/EE)             | 180 µg NGM +35 µg EE for days 1-7,<br>215 µg NGM + 35 µg EE for days 8-14,<br>250 µg NGM + 35 µg EE for days 15-21 |

The overview of these studies is displayed in the table:

| Study Ref. No. | Dose per patch NGMN/EE                              | Duration of Treatment (1 cycle = 28-day menstrual cycle unless stated otherwise) | No. of Patients evaluable for efficacy (safety) | Design* | Comparator Treatment                       |
|----------------|-----------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------|---------|--------------------------------------------|
| CONT-001       | 3.0 mg NGMN / 0.38 mg EE/                           | 4 cycles                                                                         | 148 (153)                                       | OL, PG  | 250µg NGM/35µg EE                          |
| CONT-005       | 4.5 mg NGMN / 0.56 mg EE/ 6.00 mg NGMN / 0.75 mg EE | 9 cycles                                                                         | 152 (157)                                       | DB, PG  | Placebo                                    |
| CONT-006       | 6.00 mg NGMN / 0.75 mg EE                           | 6 cycles                                                                         | 146 (150)                                       | OL, PG  | 150 µg DSG + 20 µg EE and LNG/EE triphasic |
| CONT-007       | 6.00 mg NGMN / 0.75 mg EE                           | 3 cycles                                                                         | 99 (99)                                         | OL, PG  | 150 µg DSG + 20 µg EE and LNG/EE triphasic |
| CONT-008       | 6.00 mg NGMN / 0.75 mg EE                           | 4 cycles and one 10-day cycle                                                    | 36 (36)                                         | OL      | 100µgLNG + 20 µg EE LNG/EE triphasic       |
|                | 6.00 mg NGMN / 0.75 mg EE                           |                                                                                  | 16 (16)                                         |         | 100µgLNG + 20 µg EE LNG/EE triphasic       |
|                | 6.00 mg NGMN / 0.75 mg EE                           |                                                                                  | 52 (52)                                         |         | 100µgLNG + 20 µg EE LNG/EE triphasic       |
|                | 6.00 mg NGMN / 0.75 mg EE                           |                                                                                  |                                                 |         | 100µgLNG + 20 µg EE LNG/EE triphasic       |
|                | 6.00 mg NGMN / 0.75 mg EE                           |                                                                                  |                                                 |         | 100µgLNG + 20 µg EE LNG/EE triphasic       |

OL = Open-label, DB = Double blind PG = Parallel group,

In study CONT-001, subjects received one of the three patch regimens (10 cm<sup>2</sup> [3.0 mg NGMN/0.38 mg EE], 15 cm<sup>2</sup> [4.5 mg NGMN/0.56 mg EE], or 20 cm<sup>2</sup> [6.0 mg NGMN/0.75 mg EE, EVRA]). This study also allowed for the determination of the dose. The results will be further presented under clinical efficacy. In the other studies, the patch of EVRA was used.

- *Hypothalamic-pituitary-ovarian axis*

The effect of EVRA on ovarian function was determined from serum concentrations of endogenous ovarian steroids and gonadotrophins and by analysis of follicular development using ovarian ultrasound for at least 2 cycles as recommended by the CPMP Guideline on clinical investigation of steroid contraceptives in women (CPMP/EWP/519/98).

Results were compatible with the assumption that the primary mechanism of action of EVRA is the inhibition of ovulation through gonadotrophin suppression by estrogenic and progestagenic effects of EE and NGMN, i.e, EE inhibits the secretion of FSH while the progestagenic component inhibits the release of LH.

Data on follicular activity collected from studies CONT-001 and 008 indicated that the rate of persisting follicles during treatment with EVRA did not unfavourably compare with that noted for the comparators.

Data relating to the return of ovarian function were reported with EVRA in CONT-008. The mean levels of FSH, LH and estradiol returned to near baseline both immediately post-treatment and at 4-6 weeks post-treatment. Mean levels of progesterone remained low immediately post-treatment but had risen to 14.0 nmol/l at 4-6 weeks post-treatment. No return to fertility studies were conducted but in the pivotal studies 6 pregnancies post-therapy were reported, for which the conception was estimated to have occurred after the last cycle of study medication. Therefore it was considered that EVRA would have a similar effect to oral contraceptives with respect to return to fertility.

- *\*Effects on cervical mucus*

Effects of EVRA on cervical mucus, evaluated by means of a total cervical mucus score (based on individual scores for ferning, spinnbarkeit, viscosity, quantity, cell count and pH) showed a reduction in the number of good scores (10 and above) and an increase in the number of poor scores (less than 5) compared to baseline, comparable with that observed for treatments 150 µg DSG/20 µg EE and LNG/EE triphasic.

### *\*Endometrial Effects*

Effects of EVRA on the endometrium, evaluated by means of endometrial biopsies taken at day 7 or day 14 of cycles 1 and 3, showed a mild or moderate progestational effect not different from that observed with the oral comparators 150 µg DSG/20 µg EE and LNG/EE triphasic.

### *\*Other Endocrine Parameters*

In Study CONT-008, a number of endocrine parameters were assessed in blood samples pre-study, on-therapy, and post-study for EVRA and comparators. The parameters of follicle stimulating hormone (FSH), luteinising hormone (LH), dehydroepiandrosterone sulphate (DHEA-S), estradiol, and progesterone showed a similar pattern of changes for all treatment groups with suppression of the hypothalamic-pituitary-ovarian axis, the hallmark of hormonal contraception.

Thyroid parameters such as Total Thyroxine, Free Thyroxine Index, and Thyroxine binding globulin (TBG) were assessed for all treatments. EVRA increased more the levels of TBG and Total Thyroxin as compared to the oral regimens. There was no concomitant substantial difference in relation to the Free Thyroxine Index. The levels of sex hormone binding globulin (SHBG) were also statistically significantly higher in the EVRA group than in 100 µg LNG + 20 µg EE or LNG/EE triphasic.

The increase in corticoid binding globulin (CBG) levels was similar between EVRA and the other three oral contraceptive comparators. These results indicated that the estrogenic effect of EVRA on the hepatic synthesis of CBG is the same as comparators.

Pharmacodynamic effects of EVRA on blood coagulation have been compared versus comparator 150 µg DSG/ 20 µg EE and comparator LNG/EE triphasic over a treatment period of 6 cycles in study CONT-006. No significant differences were found for FDP [fibrin degradation products, d-dimer (fibrin turn-over)] between treatments. Effects of EVRA on haemostatic parameter prothrombin fragment 1+2 was more pronounced than noted for comparators 150 µg DSG/ 20 µg EE and comparator LNG/EE triphasic, whereas for PAP [plasmin- $\alpha_2$  -antiplasmin complex (profibrinolysis)] this was the other way round. All mean changes remained within the normal range.

Results from studies CONT-005 and 006 showed that exposure to pharmacological doses of EE and NMGM resulted in the same effect on hepatic metabolism of serum parameters e.g procoagulatory, anticoagulatory and fibrinolytic factors or lipoproteins/lipids whether given orally or transdermally. Overall, these studies showed that EVRA has the same contraceptive action as the comparative combined oral contraceptives. The choice of the comparators was well justified.

### **Pharmacokinetics**

The EVRA patch was developed to give steady-state serum concentrations of NGMN and EE similar to the ones obtained with the COC containing 250 µg NGM + 35 µg EE and the triphasic COC containing NGM/EE. These two comparators have been associated with clinical efficacy. The values that covered 90 % of the subjects in these pharmacokinetic studies (excluding the 10 % with extreme values) were used as target ranges in the development of EVRA. The target concentration ranges for NGMN and EE were from 0.6 – 1.2 ng/ml and 25 - 75 pg/ml, respectively. As EVRA patch is intended to be worn for a 7-day period (168 hour), these target concentrations should, ideally, be achieved shortly after application of the patch, and then maintained until the end of this period of time.

The pharmacokinetic profile of EVRA was determined after single and multiple applications of the patch in healthy female volunteers. With the exception of a pilot pharmacokinetic study (PHI-001), which evaluated a 20 cm<sup>2</sup> patch containing 6.0 mg of NGMN and 0.6 mg of EE, all the pharmacokinetic studies used EVRA (6.0 mg NGMN/0.75 mg EE, 20 cm<sup>2</sup> patch), delivering approximately 150 µg norelgestromin and 20 µg ethinyl estradiol per day).

The results from 10 pharmacokinetic studies, including one interaction study with tetracycline (PHI-012), were provided. No direct pharmacokinetic comparison has been made between EVRA and the COC containing 250 µg NGM + 35 µg EE, but the results from the pharmacodynamic study CONT-001 compared the serum levels in women using contraceptive EVRA patches with those achieved with

this COC. The applicant agreed to perform, however, a pharmacokinetic comparing EVRA with this COC, the results of which would be submitted post-authorisation.

Additionally, a population pharmacokinetic analysis and missed patch simulation were carried out on pooled pharmacokinetic data.

## **Absorption**

### *Single application (7 day wear)*

After application of EVRA patch, plateau concentrations for NGMN ( $0.65 \pm 0.20$  ng/ml) and EE ( $38.1 \pm 12.7$  pg/ml) were reached by 48 hours and were maintained during most of the 7-days wear period. NG, which is the metabolite of NGMN, did not reach steady state due to EE-mediated induced sex hormone binding globulin (SHBG) levels to which NG is extensively bound. Following removal of the patch the mean half-lives were approximately 24 hours for NGMN, 39 for hours NG and 17 hours for EE.

In a bioavailability study, the mean (SD) absorbed dose of NGMN was 139 (44.1)  $\mu\text{g/day}$  when the patch was applied on the abdomen and 159 (28.1)  $\mu\text{g/day}$  when the patch was applied on the buttock, with an overall mean absorbed dose of 149  $\mu\text{g/day}$ . The mean (SD) absorbed dose of EE was 18.3 (7.23)  $\mu\text{g/day}$  from the abdomen and 22.9 (5.08)  $\mu\text{g/day}$  from the buttock, with an overall mean absorbed dose of 20.5  $\mu\text{g/day}$ . So a small increase in exposure was observed after application of the patch on the buttock compared with the abdomen.

In another study assessing the influence of the application sites, the mean  $C_{ss}$  for NGMN and EE were within defined target ranges (0.6 – 1.2 ng/ml for NGMN and 25 – 75 pg/ml for EE) for each anatomical site (abdomen, buttock, upper outer arm and upper torso). In addition the mean values  $\pm$  one standard deviation were very close to the limiting values that were pre-set for the ranges. This confirms that all these sites can be used as methods of application as recommended in the Summary of Product Characteristics.

The evaluation of the relationship of the patch size and the amount of steroid hormones delivered for NGMN showed that the 10  $\text{cm}^2$  patch (3.0 mg NGMN/0.38 mg EE) led to a statistically significant higher size-normalised  $\text{AUC}_{0-240\text{h}}$  and  $C_{ss}$ , compared to the 15  $\text{cm}^2$  (4.5 mg NGMN/0.56 mg EE) and 20  $\text{cm}^2$  patch (EVRA patch). No such treatment effects were observed for NG or EE. Therefore, although the 10, 15, and 20- $\text{cm}^2$  patches were directly dose proportional for NG and EE, for NGMN, the smallest patch size produced a slightly more than linear exposure and the 20  $\text{cm}^2$  size patch reached the target range.

### *Multiple applications*

When EVRA was used sequentially for 2 weeks (application on the lower abdomen), the mean concentrations for NGMN and EE approached the target range at approximately 24 hours after first application, then reached peak concentration at approximately 72 hours and remained within defined target ranges. After patch replacement, the serum concentrations of NGMN and EE dropped slightly during the first 6 hours but the concentrations remained within the target ranges. After extended wearing of a patch by three days, the serum concentrations remained within the target ranges. Based on these results it was agreed to set a margin period of two days of extra wear of the patch, in case the patient has forgotten to make a scheduled change, as mentioned in the Summary of Product Characteristics.

When EVRA was used for 3 cycles of 3-week wear (application on the abdomen or buttock) followed by one week free of patch, the serum concentrations of NGMN and EE during the 2<sup>nd</sup> and 3<sup>rd</sup> weeks remained constant or were only slightly increased compared to week 1 indicating that each previous month's treatment was effectively cleared from the body during the one-week patch-free period. Steady-state conditions were achieved during application of EVRA for three weeks per cycle. Larger increases in serum concentrations were seen for NG, especially during the first cycle. This is likely to be due to the induction of SHBG by EE and the NG-SHBG binding. Intra-subject variability ranged from 18 % to

29 % for all analytes and application sites. Inter-subject variability for NGMN and NG appeared to be somewhat greater from the abdomen (44 % - 66 %) than from the buttock (24 % - 36 %). For EE inter-subject variability from both sites ranged from 26 % to 31 %. Overall, however levels of NGMN, NG and EE appeared to be relatively consistent, both for any given subject, and between subjects and application sites.

### **Distribution**

Studies on the binding of NGMN and NG were previously performed and reviewed. In summary, both NGMN and NG are highly bound (> 98 %). NGMN is predominantly bound to albumin, and this low affinity/high capacity binding is not affected by the increases in SHBG concentrations that occur during the repeated administration of EE-containing preparations. In contrast, NG is bound predominantly to SHBG and to a much lesser extent to albumin.

Plasma albumin is the main binding protein for EE as described in the literature.

### **Metabolism and Excretion**

Since NGMN is formed as the major primary metabolite during the oral absorption of NGM, no new studies on its metabolism and excretion in humans have been presented. In summary *in vitro* studies confirmed that the initial formation of NGMN occurs in the gut wall and the further metabolic deacetylation occurs in the liver. A secondary hydrolysis of the oxime group leads to the formation of NG, which is also an active metabolite.

Based on published data for other compounds, it was considered unlikely that the metabolism for NGMN and EE would differ significantly between oral and transdermal administration, in particular with regard to any significant first-pass elimination after transdermal application.

Renal and fecal pathways eliminate the metabolites of NGMN and EE.

### **Other studies**

The effects of environmental conditions were evaluated in healthy women using EVRA patch on the abdomen over seven days, during three treatment periods, each separated by a one month washout period. Using the patch under different conditions of cold, heat, humidity and exercise did not affect the transdermal absorption and pharmacokinetics of NGMN and NG. An increased absorption was seen for EE with sauna, whirlpool and treadmill exposure, but  $C_{ss}$  remained within the target range.

A population pharmacokinetic analysis was carried out on data of NGMN and EE obtained from 230 women who received EVRA applied on the abdomen (n = 165) or on the buttock (n = 98). Increase in age, body weight, and body surface area was associated with statistically significant trends towards slightly decreasing  $C_{ss}$  and AUC values. Increasing age by 5 years (starting from 30 years) is predicted to reduce  $C_{ss}$  and AUC of NGMN and EE by approximately 5-6 %. Increasing body weight by 10 kg (starting from 65 kg) is predicted to reduce  $C_{ss}$  and AUC of NGMN and EE by approximately 8 %. Increasing body surface area by 0.3 m<sup>2</sup> (starting from 1.7 m<sup>2</sup>) is predicted to reduce  $C_{ss}$  and AUC of NGMN and EE by approximately 6 %. Race had no significant effect on  $C_{ss}$  and AUC of EE, while in Asian subjects compared to Caucasians; slightly higher  $C_{ss}$  values for NGMN were predicted.

A pharmacokinetic simulation model was developed in order to estimate how dosing irregularities may affect serum levels of NGMN and EE. The recommendations formulated on the results are considered adequate to support the advice included in the Summary of Product Characteristics, which are given in case EVRA is not used according to the recommendations and in case a back-up contraception is needed.

### **Interactions**

Although no study has been performed, no interaction between NGMN and EE is expected. In addition an *in vitro* study, indicated a low potential for metabolic interactions, both between NGMN and EE and their effects on co-administered substances.

The potential for the antibiotic tetracycline to interfere with the bioavailability of EVRA was investigated in 24 women to evaluate whether the interaction profile with a transdermal contraceptive such as EVRA could be different to that of oral contraceptives (interaction occurring within the gastrointestinal tract). Doses of 500 mg q.i.d. (2 g/day) were administered 3 days prior to, and 7 days during, the wearing of EVRA. No interaction was found with concomitant administration with tetracycline.

No specific interaction studies with products metabolised through the hepatic microsomal system were carried out but the well-known interactions have been adequately included in the Summary of Product Characteristics.

Interactions between *Hypericum perforatum* (St John's Wort) and some medicinal products, including oral contraceptives, have been reported either as case reports or as pharmacokinetic data. These interactions are most likely related to the induction of certain isoenzymes of the cytochrome P450 system by *Hypericum perforatum*. These interactions may lead to a reduction in plasma concentrations and hence to a loss of contraceptive effect. Therefore EVRA should not be used concomitantly with products containing *Hypericum Perforatum* as mentioned in the Summary of Product Characteristics.

### **Special populations**

No formal studies in patients with renal and/or hepatic impairment have been performed. Therefore EVRA is contraindicated in patients with hepatic impairment and should be used with caution in case of renal impairment, as recommended in the Summary of Product Characteristics.

The pharmacokinetic profile of EVRA has not been evaluated in children nor in adolescents.

### **Clinical efficacy**

The clinical efficacy with EVRA was evaluated in three main studies:

- CONT-3: phase III active control studies where EVRA was compared to the monophasic oral contraceptive: Desogestrel/EE (150 µg DSG + 20 µg EE).
- CONT-4: phase III active control studies where EVRA was compared to a triphasic oral contraceptive. LNG/EE (50 µg LNG + 30 µg EE for days 1-6; 75 µg LNG + 40 µg EE for days 7-11, 125 µg LNG + 30 µg EE for days 12-21).
- CONT-002: open label study

These three studies together provided contraceptive data with EVRA in 22,160 cycles in over 3,300 adult women who wore the patch for an intended duration of either 6 or 13 cycles.

In addition, the phase II study CONT-001 previously described provided data on the dose.

The clinical trials were performed according to GCP standards and agreed international ethical principles.

### **Dose response selection**

The dose finding strategy was based on previously conducted oral dose-finding studies of NGM/ EE. These studies established the dose and ratio of NGM (and NGMN) and EE which was found to be effective and safe as the oral contraceptive 250 µg norgestimate (NGM)/35 µg EE.

The selection of the EVRA patch was based on pharmacokinetic and pharmacodynamic considerations. As previously mentioned in a pharmacokinetic study where several sizes were tested, it was shown that the 20-cm<sup>2</sup>-size patch containing 6.0 mg of NGMN and 0.75 mg of EE reached the target range.

Results from study CONT-001 showed that, although the steady state was not confirmed, it appeared that based on the serum concentration of EE and NGMN, the 20 cm<sup>2</sup> patch containing 6.0 mg of NGMN and 0.75 mg of EE was the one that provided serum concentrations closer to those attained with the oral comparator. This study showed also that the 20 cm<sup>2</sup> patch releasing an average daily rate of NGMN of 150 microgram and EE 20 microgram, over a normal period of 7 days, resulted in an adequate suppression of ovulation and ovarian function and favourable bleeding pattern. This appeared to be in the range of that noted for the oral 250 µg NGM/35 µg EE

### Main study(ies)

The overview of the main studies is displayed in table 1:

Table 1

| Study                                                                                                  | Design                                    | N of patients                                            | Treatment | Comparator (COC containing)                                                                                 | Cycle                                                           | Parameters                                                                                           |
|--------------------------------------------------------------------------------------------------------|-------------------------------------------|----------------------------------------------------------|-----------|-------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| CONT-003<br>EU, S-Africa<br>1997-1999                                                                  | Open-label,<br>randomised,<br>multicentre | 1517 enrolled<br>846 took EVRA<br>643 took comparator    | EVRA      | 20 µg EE/<br>150 µg desogestrel                                                                             | 13 cycles (1/3 of<br>subjects)<br>6 cycles (2/3 of<br>subjects) | Contraception<br>Cycle control<br>Compliance<br>Safety<br>Subject<br>satisfaction<br>Skin irritation |
| CONT-004<br>US, Canada<br>1997-1999<br><br><i>Published in<br/>JAMA 2001;<br/>May 9:2347-<br/>2354</i> | Open-label,<br>randomised,<br>multicentre | 1495 randomised<br>1417 took EVRA<br>605 took comparator | EVRA      | 30 µ EE/50 µ g LNG (days 1-<br>6), 40 µ g EE/40 µg LNG<br>(days 7-11), 30 µ g EE/125 µg<br>LNG (days 12-21) | 13 cycles (1/3 of<br>subjects)<br>6 cycles (2/3 of<br>subjects) | Contraception<br>Cycle control<br>Compliance<br>Safety<br>Subject<br>satisfaction<br>Skin irritation |
| CONT-002<br>US, Australia,<br>EU, Israel<br>1997-1999                                                  | Non-<br>controlled,<br>multicentre        | 1754 enrolled<br>1672 took EVRA                          | EVRA      | -                                                                                                           | 13 cycles (1/3 of<br>subjects)<br>6 cycles (2/3 of<br>subjects) | Contraception<br>Cycle control<br>Compliance<br>Safety<br>Subject<br>satisfaction<br>Skin irritation |

### **Study design**

The objectives, entry criteria, treatment and evaluation schedules employed in the three Phase III studies were similar; most of the differences between studies were related to the inclusion of a comparator in studies CONT-003 and CONT-004.

The major entry criteria were:

- Healthy adult females, 18 to 45 years old, with an acceptable body mass index, who were sexually active and at risk of pregnancy;
- Regular menses occurring every 25 to 35 days;
- Sitting systolic blood pressure of <140 mmHg, and diastolic BP of <90 mm Hg;
- Subjects not pregnant, and/or who had completed their last term pregnancy at least 42 days prior to study medication, not breast-feeding, and with at least one normal menstruation period since their last pregnancy;
- Subjects who agreed to use only the assigned study compound for contraception during the study period, except when back-up contraception against sexually transmitted diseases was required.

In all three studies, the first application of the EVRA patch or the first tablet of the combined oral contraceptive was to be taken on the first day of the menses regardless whether they were fresh starters or oral contraceptive switchers. In all three studies EVRA patch was applied for a full week for three consecutive weeks (days 1-7, days 8-14, days 15-21 of each cycle). Days 22-28 of each cycle were patch free. Subjects assigned to either comparator groups took one tablet per day for 21 days, followed by 7 days of no treatment (CONT-003) or inactive treatment (CONT-004).



If the changing of a patch was missed by 3 days, the worn patch was to be replaced by a new patch and back-up contraception was to be used for 1 week. If 4 days or more missed changing a patch, the worn patch was to be replaced and a new patch cycle was to begin immediately with back-up contraception for one week.

A concern was raised with respect to the open-label design of the studies. It was however acknowledged that a double blind design would have been complicated considering the different routes of administration between EVRA and the comparators. The percentage of subjects using back-up contraception between EVRA and the oral comparators was not clearly different. In study CONT-003, 7.9 % of women used back-up contraception in 1.5 % of cycles with EVRA compared to 8.9 % of women who used back-up contraception in 1.7 % of cycles with 150 µg DSG/ 20 µg EE. In study CONT-004, 14.7 % of women used back-up contraception in 2.9 % of cycles with EVRA compared to 17 % of women who used back-up contraception in 4.0 % of cycles with LNG/EE triphasic. These data suggest therefore that women using EVRA were not extra careful, which gives reassurance on the absence of bias of the results.

### Efficacy parameters

The primary endpoint was the completion of the studies without becoming pregnant. According to the CPMP guideline already referred to, pregnancy rates are described by both the overall Pearl Index (for an intention-to-treat population) and life table analysis (for intention-to-treat and method failure using a multiple decrement life table procedure). Additional efficacy analyses for the overall Pearl Index included the relative risk, i.e. the ratio of the relative risk on-therapy pregnancy in the treatment group relative to the reference group for an intention-to-treat and method failure with 95 % confidence limits. The endpoints of interest were considered the 6-cycle and 13-cycle gross cumulative probabilities of pregnancy.

Based on documentation by the investigator, each “on-therapy” pregnancy was classified as either a method or a user failure. An occurrence of pregnancy was designated as a user failure if there was documentation that the subject had not taken her test compound correctly at the estimated time of conception.

Statistical considerations were to include all subjects who were assigned to treatment, received treatment for at least one day, and were not pregnant at the start of cycle 1 in the evaluation of contraceptive efficacy. Cycles following a cycle in which a pregnancy occurred were not included in the computation of the Pearl Index.

Other endpoints included cycle control analysis (proportion of subjects who experienced breakthrough bleeding and/or spotting at cycle 3), compliance and patch wearability and gastro-intestinal complaints.

## **RESULTS**

Data from subjects assigned to treatment with EVRA patch in the pivotal studies were pooled for the purpose of presenting an overall analysis of contraceptive efficacy.

### *Patient disposition*

The demographic and baseline characteristics of efficacy evaluable subjects were similar across the three pivotal studies and within studies comparing subjects with EVRA to those who received the oral contraceptives or placebo. The mean age was 28.5 years. Regarding the race, the population was predominantly Caucasian (in study CONT-003: 96 % in EVRA group and 95 % in COC containing 150 µg DSG/ 20 µg EE group; in CONT-004: 85 % in EVRA group and 84 % in triphasic COC containing LNG/EE group). Seventy six percent were non-smokers. The mean weight was 62-65 kg, without differences among studies.

As the clinical programme was initiated before the previously referred CPMP guideline came into force, a description of the baseline characteristics factors so as to see whether one of the aspects have

had an influence on the efficacy was not performed as recommended. It was however considered acceptable, as the data would have led to similar conclusions on efficacy and safety.

### Withdrawals

Overall, 26 % of all subjects withdrew prematurely from the studies.

In study CONT-003, the incidence of premature withdrawal was 19.9 % in the EVRA group and 14.5 % in the 150 µg DSG/20 µg EE group. In study CONT-004, this incidence was 29.6 % in the EVRA group versus 24.3 % in LNG/EE triphasic group. Overall, the incidence of premature withdrawal from EVRA was highest for adverse events and subject choice.

### Contraceptive efficacy

Altogether these studies provided contraceptive data with EVRA in 22,160 on-therapy cycles in over 3,319 women. Out of 3,319 women available for evaluation of efficacy, 613 women completed treatment for 13 cycles. The number of cycles was considered sufficient, i.e. the difference between the point estimate (ITT/overall Pearl Index) and the upper limit of the 95 % confidence interval does not exceed 1 and the duration of investigation is sufficient.

The results from these studies are displayed in table 2.

Table 2: Primary Efficacy Data from the Clinical Studies

| Study group                                                                             | CONT-002<br>EVRA     | CONT-003<br>EVRA     | CONT-003<br>150 µg<br>DSG + 20<br>µg EE | CONT-004<br>EVRA     | CONT-004<br>LNG/EE<br>triphasic | All subjects<br>receiving<br>EVRA |
|-----------------------------------------------------------------------------------------|----------------------|----------------------|-----------------------------------------|----------------------|---------------------------------|-----------------------------------|
| Number of Subjects                                                                      | 1664                 | 844                  | 643                                     | 811                  | 605                             | 3319                              |
| No of cycles                                                                            | 10994                | 5921                 | 4667                                    | 5240                 | 4167                            | 22,155                            |
| Number of Pregnancies – overall                                                         | 6                    | 4                    | 2                                       | 5                    | 7                               | 15                                |
| Number of pregnancies – method failure                                                  | 5                    | 3                    | 1                                       | 4                    | 4                               | 12                                |
| Overall Pearl Indices (95 % CI)                                                         | 0.71<br>(0.14, 1.28) | 0.88<br>(0.02, 1.74) | 0.56<br>(0, 1.33)                       | 1.24<br>(0.15, 2.33) | 2.18<br>(0.57, 3.80)            | 0.88<br>(0.43, 1.32)              |
| Pearl indices – method failure (95 % CI)                                                | 0.59<br>(0.07, 1.11) | 0.66<br>(0, 1.40)    | 0.28<br>(0, 0.83)                       | 0.99<br>(0.02, 1.96) | 1.25<br>(0.02, 2.47)            | 0.7<br>(0.31, 1.10)               |
| Probability of Pregnancy (overall)<br>From life table estimate to Cycle 13 (95 % CI)    | 0.7 %<br>(0, 1.4%)   | 0.5 %<br>(0, 1.0%)   | 0.3 %<br>(0, 0.8%)                      | 1.3 %<br>(0, 2.7%)   | 1.8 %<br>(0.2, 3.4%)            | 0.8 %<br>(0.3, 1.3%)              |
| Probability of Pregnancy (method failure) from life table estimate to Cycle 13 (95% CI) | 0.4 %<br>(0, 0.7)    | 0.4 %<br>(0, 0.9)    | 0.2 %<br>(0, 0.5)                       | 1.1 %<br>(0, 2.5)    | 1.3 %<br>(0, 2.7)               | 0.6 %<br>(0.2, 0.9)               |

Overall 15 pregnancies occurred in women using EVRA, of which 12 were classified as method failures, resulting in an overall Pearl Index of 0.88 (95 % CI 0.43, 1.32) and Pearl Index for method failure of 0.7 (0.31, 1.10). The ITT and method failure Pearl indices were close, as the larger part of the pregnancies reported, 12 out of 15 pregnancies, were due to method failure. The overall probability of pregnancy calculated by life-table estimate through cycle 13 was 0.8 % (95 % CI 0.3, 1.3 %) and probability for method failure was 0.6 % (95 % CI 0.2,0.9).

The use of contraception other than the method assigned was prohibited in the three efficacy studies. Data on the use of back-up contraception due to missing days of treatment was collected. Back-up contraception was reported for 506 (2.3 %) of the 22,175 cycles. No pregnancies occurred during these cycles.

The Pearl Indices after correction from back-up contraception are the displayed in table 3:

Table 3: Pearl Indices

| Study Group                         | CONT-002 EVRA    | CONT-003 EVRA    | CONT-003 150 µg DSG + 20 µg EE | CONT-004 EVRA    | CONT-004 LNG/EE triphasic | All subjects receiving EVRA |
|-------------------------------------|------------------|------------------|--------------------------------|------------------|---------------------------|-----------------------------|
| # of cycles                         | 10,743           | 5831             | 4592                           | 5095             | 4005                      | 21,669                      |
| Overall Pearl Index (95% CI)        | 0.73 (0.15,1.31) | 0.89 (0.02,1.76) | 0.57 (0,1.35)                  | 1.28 (0.16,2.39) | 2.27 (0.59,3.96)          | 0.90 (0.44,1.35)            |
| Method Failure Pearl Index (95% CI) | 0.61 (0.0,1.14)  | 0.67 (0,1.42)    | 0.28 (0,0.84)                  | 1.02 (0.02,2.02) | 1.30 (0.03,2.57)          | 0.72 (0.31,1.13)            |

In study CONT-004, there were 5 pregnancies in 5,244 cycles (Pearl Index of 1.24) compared to 4 pregnancies in 5,921 cycles (Pearl Index of 0.88) reported in CONT-003. As evaluated by a log-rank test, the results for EVRA in these two studies were not significantly different (p-value = 0.60). The higher rate of non-compliance with the triphasic COC containing LNG/EE could explain the higher Pearl Index noted in this patient group.

As 5 of the 15 pregnancies were reported in women with a body weight equal or higher than 90 kg, a concern was raised with respect to the efficacy of EVRA in this subgroup of women. A subgroup analysis was therefore performed. When the Pearl Index was calculated based on these pregnancies for the small subgroup of subjects with either a body surface area equal or greater than 2.061 m<sup>2</sup> (n = 113) or a body weight equal or greater than 90 kg (n=83) or a body mass index equal or greater than 30.1 kg/m<sup>2</sup> (n = 223), the point estimate obtained is between 5.39-10.89 with an upper limit of the 95 % confidence interval of between 9.70-20.44 (see table 4).

| Subgroup                                 | n   | Pearl Index         |
|------------------------------------------|-----|---------------------|
| Body Surface Area ≥ 2.061 m <sup>2</sup> | 113 | 9.42 (2.00, 16.84)  |
| Body Weight ≥ 90 kg                      | 83  | 10.89 (1.35, 20.44) |
|                                          |     |                     |

The efficacy was significantly reduced but remained within the range of efficacy from other available methods. It is currently unknown whether the efficacy of oral contraceptives in this over-weighted population is as good as in women with lower body weight. Therefore it was agreed that the choice of contraceptive method for an obese woman should be made after a discussion of known risks and benefits of the available options between the woman and her healthcare provider, and that the contraceptive patch might be among the available choices, as mentioned in the Summary of Product Characteristics.

#### \* Compliance

For subjects treated with EVRA, the percentage of cycles with compliance was 90.5 % to 91.8 % in each study and 91.4 % overall. The compliance in the EVRA groups appeared to be higher in comparison with the 150 µg DSG/20 µg EE (91 % vs 88 %) and the LNG/EE triphasic group (89 % vs. 78 %). These results indicate that compliance to the dose recommendations for EVRA is at least as feasible as those for oral contraceptives. Patch wearability data indicated a low number of patches that needed replacement because they either fell off or were partly detached. Adhesion of the patch appeared not influenced by different environmental conditions.

#### \* Bleeding control

Information regarding bleeding control was adequately collected by means of daily diary cards. In the three pivotal efficacy studies a total of 21,060 out of 22,176 cycles were valid for analysis of bleeding pattern in 3,319 efficacy evaluable subjects. The incidence of breakthrough bleeding and/or spotting at Cycle 3 in patients using EVRA ranged across studies from 10.0 % to 14.1 % with an average value

of 11.6 %. As expected values were lower by Cycle 13 ranging across studies from 5.5 % to 9.2 % with an average value of 8.0 %.

For both comparative studies a similar percentage of subjects in the two treatment groups reported breakthrough bleeding or spotting at Cycle 3 (CONT-003: 14 % for EVRA versus 15 % for COC containing 150 µg DSG/20 µg EE; CONT-004: 10 % for EVRA versus 9 % for triphasic COC containing LNG/EE triphasic). Similar observations were made at each of the other cycles and there were no statistically significant differences between the treatment groups, confirming that overall bleeding patterns seen with EVRA are similar to those seen with marketed oral contraceptives.

The results of both comparative studies indicated a longer duration of menses in the EVRA groups than in the two-comparator groups, the difference being statistically significant. The absolute difference was less than one day and considered clinically not significant. Other bleeding parameters were similar between EVRA and the oral contraceptive comparators.

Follow-up of pregnancies showed that all babies born to women exposed to EVRA at the time of conception were healthy.

### **Clinical safety**

Safety data were obtained from all clinical studies. Most safety information derived from the analysis of the three Phase III studies, which includes 3,300 women who received at least one dose (one patch) of EVRA. Of these, a total of 643 women received EVRA for 13 cycles.

This population comprised predominantly Caucasians (91 %), non-smokers (76 %) women whose age ranged from 18 to 45 years (mean 28.5 years). The majority of the subjects were using oral contraceptives within the two months before the studies, including 63 % who began EVRA treatment without interruption of therapy (direct switch) and 10 % whose therapy had been stopped within 2 months of the start of EVRA treatment (indirect switch). The demographic and baseline characteristics, including prior use of oral contraceptives were similar across studies for those subjects who received EVRA and within studies for the oral contraceptive comparators employed in each of the comparative Phase III studies.

The 3,330 EVRA subjects received a total of 22,176 cycles of EVRA treatment.

#### *Discontinuations*

Of the 3,330 subjects receiving EVRA, 26 % subjects withdrew from the studies prematurely, including 12 % subjects who withdrew because of adverse events. The overall discontinuation rate due to adverse event was higher for EVRA than for 150 µg DSG + 20 µg EE group (4.5 %) and LNG/EE triphasic group (5.6 %). The most commonly reported adverse event that led to discontinuation was application site reaction (1.9 % in all EVRA subjects). Other commonly adverse events leading to discontinuation were similar to those seen with the oral contraceptives such as nausea, headache, breast symptoms.

#### *Death and Serious adverse events*

Two women died during the clinical studies (one in the EVRA group and one in the LNG/EE triphasic group); both were suicides.

Nine women experienced serious adverse events that were judged by the investigators as possibly, probably or very likely related to EVRA (pulmonary embolism following elective surgery, pulmonary embolism, menorrhagia, carcinoma *in situ* of the cervix, cholecystitis, hemiparaesthesia + hypoesthesia, migraine, suspected transient ischaemic attack), one to LNG/EE triphasic (intra-cranial hypertension), and one to 150 µg DSG/ 20 µg EE (breast carcinoma). Except for carcinoma *in situ* of the cervix, menorrhagia and cholecystitis, these adverse events led to discontinuation.

### *Adverse events*

Overall, 2,665 (80 %) of the 3,330 subjects who received EVRA in the three Phase III studies experienced at least one treatment-emergent adverse event. Most adverse events, including the most commonly reported events, were mild or moderate in severity, not serious or treatment-limiting, and most resolved either spontaneously or after appropriate treatment.

The adverse event pattern of EVRA observed indicated a general safety profile comparable with that known from oral combined contraceptives, except for breast symptoms (breast discomfort, breast engorgement, and breast pain) and application site reactions.

Breast symptoms (breast discomfort, engorgement or pain) were reported in 22 % of all subjects treated with EVRA versus 9 % with COC containing 150 µg DSG/20 µg EE and 6 % with triphasic COC containing LNG/EE. Breast symptoms were mild to moderate of intensity and occurred primarily in the first cycle, and the number of reports decreased with time. In most cases breast symptoms were not treatment limiting, i.e. 1.9 % of cases led to discontinuation in the EVRA group versus 0.2 and < 0.5 in comparators (150 µg DSG + 20 µg EE and LGN/EE triphasic respectively).

There were significantly more breast symptoms and nausea observed with EVRA than with triphasic COC containing LNG/EE in cycles 1 and 2. The differences are most pronounced in comparison with 150 µg DSG + 20 µg EE, which could be explained by the higher dose of ethinyl estradiol (33 versus 20 micrograms). For most cycles after cycle 2, there was no difference between EVRA and the comparators. As it appeared that this result could not be explained by subject discontinuations from treatment, a possible explanation could be the difference in adaptation to the different plasma profiles of the progestin and estrogen components of the patch (constant delivery) versus an oral delivery (peak and trough) leading to higher initial incidence with EVRA.

In the three pivotal safety studies 17 % of EVRA-treated subjects experienced application site reactions. However, the percentage of subjects reporting skin irritation decreased with the increased duration of EVRA therapy, with the highest incidence of skin irritation reported during Cycle 1 (3.5 %) and the lowest during Cycles 12 and 13 (0.6 and 0.7 %, respectively). The low incidence of skin irritation reported by subjects during each cycle is consistent with the percentage of EVRA-treated subjects (1.9 %) who discontinued from the Phase III studies due to application site reactions. Most of the reactions at the EVRA application sites that were reported as adverse events were mild or moderate in severity, and none of these reactions was serious. The incidence of application site reactions reported by EVRA-treated subjects was within the range of values reported for transdermal estrogen or estrogen-progestogen patches used by postmenopausal women for hormone replacement therapy.

A specific safety analysis of the subgroup of women who completed at least 13 cycles showed that the results within and across studies are similar to the overall results.

An examination of adverse event incidence by age, race, and weight revealed some differences in the incidence of various treatment-related adverse events, but the results did not suggest a notable increase in risk for any demographic subgroup who received EVRA treatment.

### ***Specific safety issues***

#### *Haemostasis*

Epidemiological studies have associated the use of COCs with an increased risk for deep venous (deep venous thrombosis, pulmonary embolism) and arterial (myocardial infarction, transient ischaemic attack) thromboembolism compared to no use.

The incidence of VTE in users of oral contraceptives with low estrogen content (<50 µg ethinyl estradiol) ranges from about 20 to 40 cases per 100,000 women years, but this risk varies according to the progestagen (for COCs containing levonorgestrel, the incidence is 20 cases per 100,000 women years). This compares with 5-10 cases per 100,000 women years for non-users. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive. This increased

risk is less than the risk of VTE associated with pregnancy, which is estimated as 60 per 100,000 pregnant women years. VTE is fatal in 1%-2% of cases.

The CPMP, in its Position Statement (EMEA/CPMP/2250/01) concluded that VTE is a rare adverse event of all combined oral contraceptives (COCs). In addition the level of this risk is low, and overall the balance of benefits and risks remains favourable with all available COCs. There is also an excess risk of VTE during the first year a woman ever uses any COCs. Finally, the increased risk of VTE associated with COCs is less than the risk of VTE associated with pregnancy. The CPMP agreed therefore on a warning to be included in the Summary of Product Characteristics of combined oral contraceptives.

In the main studies, there was one case of non-fatal pulmonary embolism and one case of non-fatal post-operative pulmonary embolism observed with EVRA.

From the current safety data, it cannot be concluded whether the risk of VTE with EVRA is similar to or different from existing combined oral contraceptives. Considering that the study population is too small, the current calculated VTE rate (59 per 100,000 women years with a confidence interval of 0 to 174) can provide no valid conclusion on the relative risk for venous thromboembolic disorders versus approved combined oral contraceptives can be drawn.

As the validity of surrogate markers for the clinical endpoint VTE (haemostatic parameters, estrogenicity) is still under discussion, no firm conclusion can be drawn from the data obtained from the pharmacodynamic studies.

It is therefore not yet known how EVRA influences the risk of VTE compared with other combined oral contraceptives. On this basis, the CPMP agreed that to include a special warning in the Summary of Product Characteristics. In addition, the applicant agreed to perform a further assessment of the risk of VTE, the results of which will be provided post-authorisation.

#### *Effects on lipid metabolism*

Investigation of the effects of EVRA on lipid metabolism in comparison with placebo, over 9 treatment cycles, did not indicate relevant deleterious effects. The net effect appeared to be neutral. This outcome was supported by the results on routine lipid parameters tested in the three pivotal Phase III studies.

#### *Supportive data*

In general, the type of adverse events observed among EVRA-treated subjects in the six supportive studies (PHI-013, CONT-001, CONT-005, CONT-006, CONT-007 and CONT-008), as well as the severity and relationship to study treatment of these events, were similar to the adverse events reported in EVRA-treated subjects in the Phase III studies. In total 326 (87 %) of the 377 EVRA-treated subjects experienced one or more treatment-emergent adverse event. Adverse events having the highest incidence were headache (37 %), breast symptoms (26 %), nausea (24 %), and upper respiratory tract infection (20 %). Most of the adverse events, including the frequently reported events, were mild or moderate in severity, and most events related to the gastrointestinal and reproductive systems were considered at least possibly related to EVRA treatment.

#### *Dermal safety and patch wearability*

Four dermal safety studies were carried out with EVRA. Overall results indicated that the application of EVRA and vehicle control patches is associated with only mild primary irritation potential. A study to investigate phototoxicity potential further demonstrated that no primary irritation occurs with EVRA use.

Over 70,000 EVRA patches were worn for contraception in the three Phase III studies. Of these, 4.7 % were replaced because they fell off (1.8 %) or were partly detached (2.9 %). The percentage of patches that fell off tended to decrease over time, i.e., 5-7 % of patches became detached at Cycle 1 whereas only 1 % became detached at Cycle 13. In each study, and overall, over 90 % of the patches were changed as scheduled. Overall and in each of the individual pivotal studies, all application sites were used. The most frequently used site of application was the buttock, followed by the abdomen, upper outer arm, and torso (excluding breast tissue).

Effects of different environmental conditions, such as heat, humidity, cold and exercise on EVRA were investigated in Study PHI-015. The 30 females participating in this study were subjected to a computer-generated sequence of activities: normal activity, sauna, whirlpool, cold water bath, treadmill and combination of all activities. One EVRA patch (< 2 %) became detached during the study. Adhesion for all others was  $\geq 90$  %, and peel force measurements were similar for all activities, with mean values ranging from 0.22 during the treadmill phase to 0.44 during combination activity (mean value during normal conditions was 0.30).

## **5. Overall conclusions, benefit/risk assessment and recommendation**

### **Quality**

The quality of EVRA has been adequately established. In general, satisfactory chemical and pharmaceutical documentation was submitted for marketing authorisation. There are no major deviations from EU and ICH requirements. The quality of this product is therefore considered to be acceptable when used in accordance with the conditions defined in the Summary of Product Characteristics. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. At the time of the CPMP opinion there were some outstanding minor quality issues which had no impact on the benefit/risk profile. The applicant committed to provide the necessary information as follow up measures within an agreed timeframe, to be fulfilled post-authorisation.

### **Preclinical**

EVRA is the first combined contraceptive for transdermal application containing the well-known ethinyl estradiol and norelgestromin, which is the primary active metabolite of norgestimate. Norgestimate is the progestagenic compound of several combined oral contraceptives already authorised. The preclinical development of EVRA was therefore based on a bridging strategy. The pharmacological/toxicological data, which were previously obtained with NGM, have been used to support the topical use of NGMN. Additional studies have only been carried out when necessary. This bridging strategy is substantiated by a number of recently performed pharmacokinetic studies.

The pharmacological profile of EE is well documented in published literature because it is the estrogenic component of many approved oral contraceptives in Europe for many years.

From the pharmacological data, it was concluded that the proposed use of NGMN as progestational component of a contraceptive could be considered as efficacious and safe as NGM.

Effects observed in the toxicity studies are mostly limited to known pharmacological effects of steroids. Local toxicity is not considered a point of concern.

### **Clinical efficacy**

EVRA has been specifically developed to generate adequate systemic levels of both active substances, comparable to already existing combined oral contraceptive NGM/EE (250 µg/35 µg). A concern was raised however on the lack of direct pharmacokinetic comparison between the two products to confirm that the exposure achieved with EVRA are in terms of NGMN, EE and NG are similar to the ones achieved with NGM/EE (250 µg/35 µg). The applicant agreed, therefore, to perform a pharmacokinetic study, the results of which would be submitted post-authorisation.

The contraceptive efficacy of EVRA is mainly substantiated by three Phase III studies in women aged 18 to 45 years, including two controlled studies where the comparators were a COC containing 150 µg desogestrel/ 20 µg ethinyl estradiol and a triphasic COC containing levonorgestrel + ethinyl estradiol. The efficacy of EVRA was demonstrated and appeared similar to that of the comparators. The efficacy of EVRA was decreased in women with a body weight equal or higher than 90 kg and

therefore the choice of contraceptive method for an obese women should be made based on the known benefits and risks of the available choices, including EVRA.

The rationale for the development of a transdermal patch was that the patch has greater acceptability of ease of compliance with dosing instructions. In the Phase III studies, the compliance in the EVRA groups appeared to be higher in comparison with COC containing 150 µg desogestrel/ 20 µg ethinyl estradiol (91 % versus 88 %) and a triphasic COC containing levonorgestrel + ethinyl estradiol (89 % versus 88 %) indicating that compliance to the dose recommendations for EVRA is at least as feasible as those for oral contraceptives.

### **Clinical safety**

There is no clinical evidence indicating that a transdermal patch is, in any aspect, safer than the existing combined oral contraceptives.

The most commonly adverse events reported with EVRA included breast symptoms with an incidence higher than with the comparators although primarily occurring during the first cycle and in most cases not leading to discontinuation, and nausea. Application site reactions were also observed, but leading to discontinuation in only 2 % cases.

It is known that the use of any combined oral contraceptives carries an increased risk for venous thromboembolism compared with no use. It is however not yet known how EVRA influences with the risk of VTE compared with other combined oral contraceptives. The CPMP agreed therefore to include a warning in the Summary of Product Characteristics and the applicant undertook to perform a further assessment of the risk of venous thromboembolism, as part of the follow-up measures to be fulfilled post-authorisation.

### **Recommendation**

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered that the benefit/risk profile of EVRA was favourable and therefore recommended in February 2002 the granting of a marketing authorisation for EVRA transdermal patch (6 mg norelgestromin + 750 µg ethinyl estradiol) for the following indication:

“Female contraception. EVRA is intended for women of fertile age. The safety and efficacy has been established in women aged 18 to 45 years”

However, potential risks and environmental implications of the disposal of a contraceptive patch containing ethinyl estradiol were brought to the attention of the CPMP. The potential environmental risk of EVRA is related to its ethinyl estradiol component, of which approximately 80 % of the 750 micrograms is not absorbed and a major portion may be retained in the disposed patches (600 micrograms ethinyl estradiol). The CPMP concluded that there is a negative impact on the environment from the use of the EVRA patch if inappropriately disposed, due to the resulting release of ethinyl estradiol in the freshwater environment.

According to the current pharmaceutical legislation, the environmental risk assessment is not a criterion to be taken into account when recommending the granting of a marketing authorisation. It foresees, however, that if applicable, reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with the indication of any potential risks presented by the medicinal product for the environment should be considered.

As a consequence, the CPMP agreed to revise the Opinion of February 2002 to include recommendations on the disposal of the used and unused patches to be included in the relevant sections of the Summary of Product Characteristics, Labelling and Package Leaflet to help protecting the environment. In addition the applicant agreed, as part of follow-up measures to the fulfilled post-authorisation, to include in the package an appropriate disposal container for used patches prior to



marketing the product in the European Union. Such a disposal container was authorised by the European Commission in February 2003.

The CPMP recommended therefore the granting of the marketing authorisation for EVRA transdermal patch (6 mg norelgestromin + 750 µg ethinyl estradiol) for the following indication:

“Female contraception. EVRA is intended for women of fertile age. The safety and efficacy has been established in women aged 18 to 45 years”. The CPMP adopted therefore the revised Opinion on 30 May 2002.