COLLEGE TER BEOORDELING VAN GENEESMIDDELEN - MEDICINES EVALUATION BOARD

PUBLIC ASSESSMENT REPORT

NuvaRing, ring voor vaginaal gebruik RVG 25073

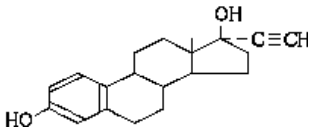
International Non-proprietary Name (INN) **ethinylestradiol/ etonogestrel**

Report version: Original (first report) Date 2002-06-19

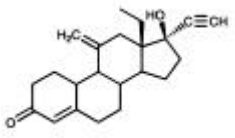
GENERAL INFORMATION

Active substances: ethinylestradiol 2.7 mg/ etonogestrel 11.7 mg

Structural formulas:



ethinylestradiol



etonogestrel

Pharmacotherapeutic group: hormonal contraceptives, progestogens and estrogens

ATC code: G03AA09

Pharmaceutical dosage form vaginal ring

Route of administration: vaginal

Therapeutic indication: contraception

Prescription information: prescription only

Marketing Authorisation Holder: N.V. ORGANON Oss, the Netherlands

Date of first application (national): 29-12-1999

Application type/legal basis: Directive 65/65/EEC, Article 4.8 (a)

Date of authorisation: 14-02-2001

Completion of Mutual Recognition Procedure (Directive 75/318/EEC): 2001-06-12
(Concerned member states: Austria, Belgium, Denmark, Finland, Germany, Greece,Iceland, Ireland, Italy, Luxembourg, Norway, Portugal, Spain and Sweden.)

ABSTRACT

On February 14, 2001 the Medicines Evaluation Board in the Netherlands issued a marketing authorisation for the medicinal product NuvaRing, a vaginal ring, composed of two types of ethylene vinylacetate copolymers (EVA). The core of the ring contains 2.7 mg ethinylestradiol (EE) and 11.7 mg etonogestrel (ENG). Both active substances are well known. The vaginal ring is a new pharmaceutical dosage form using the vaginal route of administration to achieve systemic steroid levels sufficient for contraception. The contraceptive effect of NuvaRing is primarily based on inhibition of ovulation. When placed in the vagina, the ring releases 120 µg/day of etonogestrel and 15 µg/day of ethinylestradiol over a 3-week period of use.

The approved indication is contraception. Annotations to the therapeutic indication are that NuvaRing is intended for women of fertile age and that safety and efficacy have been established in women aged 18 to 40 years. The woman herself must insert NuvaRing in the vagina. The dose recommendation is that each ring is to be used for one cycle; a cycle consists of 3 weeks of ring use followed by a one-week ring-free interval.

The Summary of Product Characteristics (SPC, part IB1 of the dossier) describes the conditions for use in detail. The SPC is adapted to the latest European opinions on the use of combined hormonal contraception.

Each vaginal ring is packed in an aluminium/polymer pouch. A commercial package consists of one or three pouches in a carton box. NuvaRing has a shelf life of two years at 2-8 °C in the Pharmacy, followed by a shelf life of 4 months stored below 30°C at the users'.

The toxicological effects of ENG and EE when administered through the vaginal route consisted mainly of expected pharmacological effects of these active substances. These effects have no special significance for human use. The majority of the special toxicity studies on leachables from the EVA copolymer were performed with EVA material from Implanon and the IUD Multiload, which has a slightly different composition than the copolymer of which NuvaRing is made. These animal studies did not reveal sensitising or irritating potential.

The efficacy and safety of NuvaRing was documented by clinical trials performed according to the recommendations of the CPMP ‘Note for Guidance on clinical investigation of steroid contraceptives in women’ (CPMP/EWP/519/98). The pivotal studies included two non-comparative phase III studies with a duration of 13 cycles. One study was performed in Europe, the other in the USA. Contraceptive efficacy, expressed as the Pearl Index, was calculated on the basis of combined study data. The Pearl Index calculated for *“typical use” (method + patient failure)*, based on Intention-To-Treat analysis of 23,297 cycles, was 1.176 (95% confidence interval: 0.728 – 1.797). The Pearl Index calculated for *“method failure”* was 0.765 (95% confidence interval: 0.367 – 1.407).

Although pharmacodynamic data indicated that inhibition of ovulation and the degree of suppression of ovarian function is in the same range as observed for the comparator (Marvelon), the combined Pearl Indices were higher than generally observed for oral monophasic combined contraceptives. These higher Pearl Indices

were in particular due to the higher pregnancy rate in the US-study in comparison with the EU-study. This difference is considered especially attributable to the higher percentage of women in the US study non-compliant with the recommended regimen in these studies. Furthermore, especially temporary removals lasting more than 3 hours occurred more often in the US study than in the European study, a situation for which no standard back-up contraception advice was given. The dose regimen currently recommended in the SPC is much stricter than the recommendations used in the clinical studies. The product information now advises against temporary removals, i.e. once inserted, the ring is left in the vagina continuously for 3 weeks. In case the ring has been out of the vagina for more than 3 hours, a supplementary barrier method should be used for 7 days.

The observed bleeding pattern fell within the range of that known for oral combined hormonal contraceptives. The same applies to effects on haemostasis, lipid- and carbohydrate metabolism that were investigated in a comparative design versus an oral contraceptive containing 150 µg levonorgestrel and 30 µg ethinyl estradiol.
The adverse event pattern was not clearly different from that known for oral combined hormonal contraceptives, except for device-related problems (e.g. expulsion, coital problems, and foreign body feeling), which were mentioned by 2.4% of all users. Specific investigation of local safety by means of cervix smear, microbiological investigation and colposcopy did not reveal a negative effect on a local level. A potential clinical advantage of an absence of daily peak concentrations of estrogen and progestogen, in terms of a more favourable adverse event pattern, remains to be established. Combined hormonal contraceptives are associated with an increased risk for venous thrombosis. Due to the limited study population in the clinical studies, the data submitted does not allow conclusions regarding the relative incidence of these rare events.

The Medicines Evaluation Board, on the basis of the quality, efficacy and safety data submitted, considered that NuvaRing can be consistently produced with sufficient quality, and efficacy for the therapeutic indication, as well as safety, has been adequately shown.

SAMENVATTING

Op 14-02-2001 heeft het College ter beoordeling van geneesmiddelen NuvaRing geregistreerd. De vaginale ring is gemaakt van twee typen ethyleenvinylacetaat (EVA). De kern van de ring bevat 2,7 mg ethinylestradiol (EE) en 11.7 mg etonogestrel (ENG). Beide werkzame bestanddelen zijn goed bekend. De vaginale ring is een nieuwe farmaceutische vorm waarbij via de vaginale toedieningsweg systemische hormoonspiegels worden bereikt in een orde van grootte noodzakelijk voor adequate anticonceptie op basis van ovulatieremming. Na plaatsing in de vagina heeft de ring een dagelijkse gemiddelde afgifte van120 µg etonogestrel en 15 µg ethinylestradiol af gedurende een periode van 3 weken.

De goedgekeurde indicatie is anticonceptie. Bij de indicatie zijn twee de kanttekeningen geplaatst in de productinformatie: ten eerste dat NuvaRing bestemd is voor vrouwen in de vruchtbare leeftijd en ten tweede dat de veiligheid en werkzaamheid zijn onderzocht bij vrouwen tussen de 18 en 40 jaar.

NuvaRing dient in de vagina geplaatst te worden voor een ononderbroken periode van drie weken, gevolgd door een ringvrije week waarna een nieuwe ring wordt geplaatst. De gedetailleerde voorwaarden voor het gebruik van het geneesmiddel staan beschreven in de Samenvatting van de kenmerken van het product (deel IB1 van het registratiedossier). De productinformatie is aangepast aan recente Europese standpunten over gecombineerde hormonale anticonceptie. Elke vaginale ring is verpakt in een sachet van geplastificeerd aluminium. De handelsverpakking is een kartonnen doos met één of drie sachets. De houdbaarheid van NuvaRing is twee jaar bij 2-8 °C in de apotheek, gevolgd door 4 maanden houdbaarheid beneden 30°C bij de gebruikster thuis.

De toxicologische effecten van vaginaal toegediend ENG en EE waren voornamelijk het gevolg van de te verwachten farmacologische werking van ENG en EE. Deze effecten hebben geen bijzondere betekenis voor het gebruik bij de mens. De meeste speciale toxiciteitstudies met uitloogbare stoffen uit EVA zijn uitgevoerd met materiaal uit het IUD Multiload, dat een iets andere samenstelling heeft dan NuvaRIng. Deze dierstudies lieten geen sensibiliserende of irriterende werking zien.

De werkzaamheid en veiligheid van NuvaRing is klinisch onderzocht volgens de aanbevelingen van de CPMP 'Note for Guidance on clinical investigation of steroid contraceptives in women' (CPMP/EWP/519/98). De voornaamste klinische documentatie bestond uit twee identieke, niet-vergelijkende fase 3-studies met een duur van 13 cycli. Eén studie is uitgevoerd in Europa, de andere in de USA. De anticonceptieve werkzaamheid, uitgedrukt als de Pearl Index (zwanger-schapscijfer), is berekend op basis van gecombineerde gegevens van de twee studies.

Op basis van een Intention-To-Treat analyse van 23297 cycli, werd een Pearl Index van 1.176 (95% betrouwbaarheidsinterval 0.728 – 1.797) berekend voor "typisch gebruik" (falen van de methode + onjuist gebruik van de methode). De Pearl Index berekend op basis van zwangerschappen die uitsluitend zijn toe te schrijven aan het falen van de methode ("method failure") was 0.765 (95% betrouwbaar-heidsinterval 0.367 – 1.407).

Hoewel farmacodynamische studies aantoonden dat de graad van ovulatie-inhibitie van dezelfde orde van grootte was als gezien bij het referentiepreparaat (Marvelon), waren de gecombineerde Pearl Indices hoger dan die men in het algemeen ziet bij orale gecombineerde monofasische anticonceptiva. Deze hogere Pearl Indices werden veroorzaakt door het hogere zwangerschapscijfer in de Amerikaanse studie. Dit verschil werd voornamelijk toegeschreven aan het hogere percentage vrouwen in de Amerikaanse studie dat zich niet strikt aan de doseringsadviezen hield. Bovendien waren er in de Amerikaanse studie meer vrouwen die de ring langer dan 3 uur uit de vagina hadden verwijderd, een situatie waarvoor niet standaard werd geadviseerd een additioneel anticonceptivum te gebruiken. Het doseringsadvies, dat nu in de SPC is opgenomen, is veel strenger dan de aanbevelingen van de klinische studies, daar tijdelijke verwijdering van de ring niet is toegestaan, c.q. na plaatsing dient de ring gedurende een periode van 3 weken onafgebroken in de vagina te blijven. Mocht de ring toch uit de vagina raken voor een periode langer dan 3 uur, dan dient gedurende 7 dagen aanvullend een barrièremiddel gebruikt te worden.

Het bloedingspatroon kwam overeen met dat gezien bij orale gecombineerde hormonale anticonceptiva. Vergelijkend onderzoek met Microgynon ter evaluatie van

effecten op bepaalde stollingsfactoren, het lipiden- en koolhydraatmetabolisme toonde geen duidelijke verschillen tussen beide producten aan.
Het bijwerkingenpatroon was vergelijkbaar met dat gerapporteerd voor orale gecombineerde hormonale anticonceptiva, met uitzondering van de lokale bijwerkingen gerelateerd aan de plaats van toediening (expulsie, problemen bij de coitus en het voelen van een vreemd lichaam) dat door 2.4% van alle gebruiksters werd gemeld. Specifiek onderzoek naar de lokale veiligheid met behulp van een cervixuitstrijk, microbiologisch onderzoek en colposcopie toonde geen negatieve effecten aan. Een mogelijk klinisch voordeel van de afwezigheid van de dagelijkse piekconcentraties van oestrogeen en progestageen, in de vorm van een gunstiger bijwerkingenpatroon, kan nog niet worden vastgesteld.

Aan orale gecombineerde hormonale anticonceptiva is een verhoogd risico van veneuze trombose toegeschreven. Vanwege de beperkte omvang van de studiepopulatie staan de gegevens geen conclusie toe over het relatieve voorkomen van een dergelijke zeldzame bijwerking bij gebruik van de NuvaRing.

Het College ter beoordeling van geneesmiddelen heeft op basis van de overgelegde gegevens geconstateerd dat NuvaRing met constante, voldoende kwaliteit kan worden geproduceerd. De werkzaamheid en veiligheid bij de gestelde indicatie zijn voldoende bewezen.

SCIENTIFIC DISCUSSSION

INTRODUCTION

NuvaRing is a vaginal ring for systemic contraception that contains ethinylestradiol and etonogestrel as active ingredients. This ring is a new pharmaceutical dosage form using the vaginal route of administration to achieve systemic steroid levels sufficient for contraception. The contraceptive effect of NuvaRing is primarily based on inhibition of ovulation.

NuvaRing is a flexible, transparent, colourless to almost colourless ring made of ethylene vinylacetate (EVA) copolymers. When placed in the vagina, the ring is claimed to release 120 µg/day of etonogestrel and 15 µg/day of ethinylestradiol over a 3-week period of use. Each ring is to be used for one cycle; a cycle consists of 3 weeks of ring use followed by a one-week ring-free interval.

The rationale for its development is that the use of NuvaRing, in comparison with orally administered contraception, does not depend on daily intake of tablets. Gastrointestinal disturbance, which may affect contraceptive efficacy, is avoided. Additionally, the absence of daily peak concentrations of estrogens and progestogens might improve the adverse event pattern. The latter could not be substantiated with the data submitted.

In the Netherlands, the vaginal route of administration is new for hormonal contraception. Only one controlled-release vaginal pessary, containing dinoprostone, is registered for the indication of cervical ripening in patients at term in pregnancy. The active ingredients of NuvaRing are not new. Etonogestrel, the active compound of Implanon, is the biologically active metabolite of desogestrel.

Desogestrel is the progestogenic component of a number of combined oral contraceptives and an oral progestogen-only contraceptive. Ethinyl estradiol is present in all registered combined oral contraceptives.

The clinical part of the registration dossier consisted of two large non-comparative clinical phase III studies, three comparative metabolic studies, three clinical pharmacology studies addressing pharmacokinetics and/or pharmacodynamics and one local effects study. All studies were conducted under GCP conditions. The phase III studies were carried out in conformity with the revised CPMP 'Note for Guidance on clinical investigation of steroid contraceptives in women' (CPMP/EWP/519/98).

CHEMICAL-PHARMACEUTICAL ASPECTS

Composition

Dosage form
The vaginal ring has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. It consists of a core surrounded with a skin. The core consists of the active substances, dissolved in ethylene vinylacetate copolymer (with 28 % vinylacetate) and magnesium stearate. The skin consists of ethylene vinylacetate copolymer (with 9 % vinylacetate). The ring releases etonogestrel and ethinylestradiol at an average amount of 0.120 mg and 0.015 mg per 24 hours, over a period of 3 weeks.

Packaging type and material
The vaginal rings are individually packed in reclosable sachets, which consist of an aluminium foil with a heat-sealed low-density polyethylene layer on the inside and a layer of polyethylene terephtalate on the outside. The sachet has a low-density polyethylene zipper.

Active substance
Ethinylestradiol complies with the Ph.Eur. -monograph and additional specifications for particle size and residual solvents. The quality of etonogestrel is checked by specifications for identity (melting point, IR and TLC), sulphated ash, heavy metals, loss on drying, related substances, residual solvents, polymorphs, optical rotation, particle size and microbial purity.

Other ingredients
Ethylene vinylacetate copolymer,-28 % vinylacetate, ethylene vinylacetate copolymer- 9 % vinylacetate and magnesium stearate are auxiliary substances. Both copolymers are checked by specifications for identity, appearance, the melt index, heavy metals, peroxide values, additives, the assay of vinylacetate monomer and the microbial purity. The specifications are more stringent than the Ph.Eur.-monograph for 'Ethylene/vinylacetate copolymers for containers and tubing for total parenteral nutrition preparations'. The magnesium stearate complies with the Ph.Eur. and is of vegetable origin.

Product development and finished product

Development pharmaceutics/ clinical trial formula
Three different prototype vaginal rings were used in the clinical trials. In the phase III studies, the rings have the composition brought on the market. The core of the

ring functions as a reservoir and its skin as a release-controller. The release rate depends on the selected dimensions. NuvaRing is robust with respect to dose dumping, because the drug substances are completely dissolved in the core, even breakage of the ring leads to a minor increase in release rate. The amount of active substances present in the ring is sufficient to guarantee a release up to 35 days; enough for an incidental use during four weeks. The ring dimensions of the final product were the best tolerated in the clinical trials.

Manufacture

The manufacture of NuvaRing strongly resembles that of Implanon (etonogestrel implant). The process consists in the preparation of the core granulate, the so-called co-extrusion process (manufacture of the skin/core fibre), the cutting of the fibre, the assembly of the ring and the packaging.

Specifications of the medicinal product

The quality of the final product is checked with respect to the following parameters.

- Appearance;
- Identity of the active substances (TLC and HPTLC);
- Weight and sizes;
- Assay of the active substances and related substances (HPLC);
- Dissolution specifications with a method, which has been developed especially to -measure the in-vitro release profile on a period of three weeks;
- Microbial quality[1].

The in vitro release is an important quality parameter. Profound validation has shown the method of analysis to be suitable. Linear correlation exists between in vitro dissolution and in vivo release of both active substances. The release diminishes in time. The maximum release at day 1, the minimum at day 21 and the average release of day 2 – 21 have been specified, to guarantee a constant product. The specification for the microbial quality is considered acceptable with respect to the route of administration. Batch analysis results on six production batches demonstrate compliance to the product specifications.

Incompatibilities

No incompatibilities of the active substances and the core material have been observed. As both copolymers are nearly identical, the compatibility with both materials is considered sufficient.

Stability of the medicinal product and shelf-life

The registered shelf life is 2 years at 2-8°C in the pharmacy, followed by 4 months stored below 30°C at the users'. Stability results have shown that during this storage period the quality of the product remains within specifications provided it is stored at the prescribed conditions. These conditions followed from the observation in stability studies that NuvaRing can physically be unstable when stored for long term periods at high temperatures.

[1] Vaginal dosage forms that are used in women with an intact vaginal epithelium do not have to be sterile, but need to be low in viable counts. NuvaRing is produced under conditions that assure a low viable count of the ring.

PRECLINICAL PHARMACOLOGICAL AND TOXICOLOGICAL ASPECTS

Introduction

Ethinylestradiol (EE) and etonogestrel (ENG) are no new active substances, however the combination of the two and their route of administration with NuvaRing are new. EE is a pharmacopoeal substance with well-established use. Hence, this report does not discuss its properties, apart from those related to the route of administration. The preclinical profile of ENG is described in the public assessment report on Implanon. The important elements of the safety assessment are the systemic and local toxicity related to the new pharmaceutical form and the pharmacokinetics of ENG and EE after application of NuvaRing.

Sizes and types of rings used in the preclinical program are different from those intended for marketing. NuvaRing is made completely of ethylene vinylacetate (EVA) copolymers, whereas in animal studies silastic or EVA-containing silastic rings were used. In other studies, ENG and EE were contained in suppositories instead of vaginal rings. Furthermore, studies were performed in the rat, dog, rabbit, mouse and guinea pig using the oral, intramuscular and intraperitoneal route. Effects of the use of the different types of material on the bioavailability have been studied.

Pharmacokinetics

Both in dogs and in monkeys maximum ENG and EE serum concentrations were reached in the first week after application of the rings. In Rhesus monkeys ENG and EE serum concentrations quickly drop to approximately half the initial concentrations after the first week. In dogs these concentrations decreased more gradually during a 3-week period. Steady state volume of distribution in dogs is 1-3 times body weight suggesting that binding of ENG to tissue is limited. ENG is extensively metabolised in humans and laboratory animals. Except for the 6β-hydroxy-13-hydroxyethyl metabolite all human metabolites were found in rats and dogs as well. After oral or subcutaneous administration of [^{3}H]-ENG to rats and dogs, most of the radioactivity is recovered within a few days post administration in urine and faeces. No difference is expected after vaginal administration. In dogs, bioavailability of ENG via the vaginal route (silastic rings) is about 1.5 times higher than that of ENG via the oral route.

Toxicology

Repeated dose toxicity

The effects of ENG and EE administered through the vaginal route either with suppositories (in Cynomolgus monkeys) or with vaginal EVA-silastic rings (in Rhesus monkeys) consisted mainly of changes in reproductive organs and, in one study, thymic involution. Local effects of ENG and EE administered with suppositories in Cynomolgus monkeys were proliferation of epithelium, keratinisation, aggregation of leukocytes, intracellular oedema, immigration of mononuclear cells, hyperaemia of papillary body with aggregation of leukocytes, histocytes and plasma cells. In Rhesus monkeys, thin vaginal epithelium, red discoloration of the vagina, and minimal to slight vascular congestion of the vagina were observed. A six-month study in Rhesus monkeys with a placebo EVA-silastic ring did not reveal adverse effects. In Cynomolgus monkeys, the compound effects were reversed after 4 weeks without treatment. The effects are considered most likely to be attributable to the pharmacological activities of the ENG and EE. The

value of the toxicity studies is limited, because systemic exposure was similar to the anticipated clinical exposure, which is generally not high enough to establish proper safety margins. However, the clinical safety of the use of ENG and EE as a contraceptive is supported by well-established safe use of other DSG / EE containing contraceptives.

Special toxicity studies

Several special toxicity studies were performed to investigate the local and systemic toxicity of leachables from EVA copolymers. Most of these studies were performed as part of the preclinical assessment of the IUD Multiload Cu-250 and Implanon. Some studies were not submitted previously. Vaginal irritation of a saline extract of IUD material was tested in rabbits and found negative. The same extract did not show sensitizing potential in guinea pigs, nor caused cell lysis in L-929 mouse fibroblasts in vitro. However, the extract of the (non-metal part of the) IUD and up to 6-fold dilutions thereof did cause complete cell growth inhibition in a L-929 mouse fibroblast cell culture. The EVA copolymer of Multiload CU-250 is slightly different from that of NuvaRIng.

CLINICAL ASPECTS

The following abbreviations appear in this chapter:

EE	ethinyl estradiol	FSH	follicle stimulating hormone
ENG	etonogestrel	LH	luteinising hormone
DSG	desogestrel	PAI-I	plasminogen activator inhibitor-I
LNG	levonorgestrel	SHBG	sex hormone binding protein
COC	combined oral contraceptive	PP	per protocol
CCVR	combined contraceptive vaginal ring	ITT	intent to treat
HPO-axis	hypothalamus-pituitary-ovarian axis	PI	pearl index
		IVRS	interactive voice response system

The clinical dossier included two large non-comparative clinical phase III studies, three comparative metabolic studies, three clinical pharmacology studies that addressed pharmacokinetics and/or pharmacodynamics and a local effects study. All studies have been conducted under GCP conditions.

Overview of clinical studies: study design, inclusion criteria and duration

Protocol	Country	Design [a]	inclusion criteria [b]	Duration [c]
34218	The Netherlands	Single centre, randomised, cross-over, comparative	healthy females, age 18-35 [i]	1 cycle [c]
34219	Europe [e]	Multi centre, non-comparative	healthy females, age 18-40	13 cycles
34220	Finland	Multi centre, Non-randomised, comparative	healthy females, age 18-40	6 cycles
34221	Iceland	Single centre, Non-randomised, comparative	healthy females, age 18-40	6 cycles

Protocol	Country	Design [a]	inclusion criteria [b]	Duration [c]
34222	UK and The Netherlands	Multi centre, randomised, comparative	healthy females, age 18-40	6 cycles
34225	The Netherlands	Single centre, randomised, cross-over non-comparative	healthy females, age 18-35 [i]	2 cycles
34226	The Netherlands	Single centre, non-comparative	healthy females, age 18-35 [i]	2 cycles [c]
068003	USA and Canada	Multi centre, non-comparative	healthy females, age 18-40	13 cycles
068004 [f]	USA	Multi centre, non-comparative	healthy females, age 18-40	13 cycles

a) All studies had an open design
b) Major inclusion criteria were: women at risk for pregnancy and asking for contraception, cycles with a usual length between 24 and 35 days and an intra-individual variation of plus or minus 3 days, body mass index =18 and =29 Major exclusion criteria were: cervicitis, vaginitis, or a bleeding erosio portionis; a cervical smear PAP IIIa or higher at screening, contra-indications for contraceptive steroids; within two months after abortion/delivery/breast feeding; within two months of use of an implant or hormone medicated IUD or within six months of use of an injectable hormonal method of contraception; prolapse of the uterine cervix, cystocele, rectocele; severe or chronic constipation; dysparenia or other coital problems.
c) The duration of the treatment with the ring is indicated, 1 cycle being a ring period of 3 weeks and a ring-free period of 1 week, except for trial 34218 (here the ring period was 35 days) and trial 34226 (the second cycle deviated from the recommended regimen).
e) Clinical centres were in Austria, Belgium, Denmark, Finland, France, Germany, Israel, Norway, Spain, Sweden, The Netherlands, and United Kingdom
f) Interim report after all women completed 6 cycles
i) The upper limit of the age range was more restricted in the PK/PD studies, to avoid possible inclusion of pre-menopausal women

Overview of clinical studies (continued): number of subjects, comparators and objectives

Trial	NuvaRing			Comparator	Objectives		
Protocol	N [d]	Cycles	WY [d]		Pharmaco-kin/ pharmaco-dymamics	Efficacy, safety, vaginal bleeding	Specific safety
34218	16	16	1.58	oral DSG/EE (150µg/30µg) I.V. ENG/EE (150µg /30 µg)	X	X [g]	
34219	1,145	12,109.4	928.31	-		X	
34220	40	215.5	16.52	LNG/EE (150 µg /30 µg)		X	lipid metabolism
34221	44	216.5	16.60	LNG/EE (150 µg /30 µg)		X	coagulation and fibrinolysis

Trial	NuvaRing			Comparator	Objectives		
Protocol	N [d]	Cycles	WY [d]		Pharmaco-kin/ pharmaco-dymamics	Efficacy, safety, vaginal bleeding	Specific safety
34222	37	202.5	15.52	LNG/EE (150 µg / 30 µg)		X	Carbohydrate metabolism, adrenal and thyroid function
34225	24	37.6	2.88		x	X [g]	
34226	45	61.1	4.68		x	X [g]	
068003	1,177	11,188.	857.68			x	
068004 [f]	58	460.4	35.29			x	local effects
TOTAL	2,586	24,507.1	1,879.06				

d) N=All-SubjectsTreated group, WY= women years

g) Efficacy was not studied in these trials

Pharmacokinetics

Etonogestrel, the active metabolite of desogestrel, which is completely metabolised in the gut wall and liver, is the biologically active ingredient of Implanon. . The pharmacokinetics of both active ingredients has been investigated in two studies. In one study the pharmacokinetics are compared with Marvelon (oral DSG/EE 150µg/30µg) and an intravenous injection of both compounds. The other study investigated the interaction with a spermicide and an antimycotic.

Absorption

Bioavailability
The bioavailability and the pharmacokinetics of ENG and EE released from the CCVR were compared with those after administration of Marvelon and with an intravenous administration of both active substances. The study was conducted in two parallel groups, each on Marvelon treatment for at least one cycle before the start of the trial in eight healthy females.

Etonogestrel characteristics

	NuvaRing (during 1 cycle CCVR)	Marvelon (at day 21)	Intravenous (after 1 dose)
Dose mg/day	0.12 mg (claimed)	0.15 mg as desogestrel	0.15 mg
T_{max} (h)	200 ± 70 (after day 1)	1.3 ± 0.8	n.a.
C_{max} (pg/mL)	1716 ± 445	4273 ± 830	10298 ± 2585
C_{min} (pg/mL)	n.a.	1004 ± 405	n.a.
C_{ss} (pg/mL)	n.a.	1617 ± 491	n.a.
AUC_{0-35d} (ng.h/mL)	1139 ± 265		
AUC_{0-inf} (ng.h/mL)	1182 ± 278	38.8 ± 11.8	50.8 ± 15.6
$T_{1/2}$ (h)	29.3 ± 6.1	30.1 ± 5.1	28.4 ± 3.4
Clearance (L/h)	3.35 ± 0.8	4.37 ± 1.2	3.65 ± 0.9
Bioavailability (%)	103 ± 13	79.2 ± 7.7	100

Ethinylestradiol characteristics

	NuvaRing (during 1 cycle CCVR)	Marvelon (at day 21)	Intravenous (after 1 dose)
Dose mg/day	0.015 mg (claimed)	0.030 mg	0.030 mg
T_{max} (h)	59 ± 67 (after day 1)	1.18 ± 0.39	n.a.
C_{max} (pg/mL)	34.6 ± 17.4	125 ± 46	598 ± 191
C_{min} (pg/mL)	n.a.	17.2 ± 7.0	n.a.
C_{ss} (pg/mL)	n.a.	34.4 ± 10.7	n.a.
AUC_{0-35d} (pg.h/mL)	15254 ± 3536		
AUC_{0-inf} (pg.h/mL)	15944 ± 4423	827 ± 258	1939 ± 824
$T_{1/2}$ (h)	44.7 ± 28.7	29.5 ± 16.7	37.1 ± 20.0
Clearance (L/h)	34.7 ± 11.6	39.6 ± 12.2	19.0 ± 4.9
Bioavailability (%)	55.6 ± 12.9	53.8 ± 17.6	100

Comparison of the ENG concentrations for the CCVR after one week (1.5 ng/mL) with mean concentrations after administration of Marvelon (1.6 ng/mL) showed similar levels. In the following weeks, steady state levels of ENG after application of the CCVR were lower than after treatment with Marvelon. The average EE concentrations during CCVR use (about 18 pg/mL) are lower than the average steady state concentrations for Marvelon (34 pg/mL) but are comparable with the C_{min} concentrations after administration of Marvelon. No statistically significant differences were found with respect to the half-lives between the three routes of administration for both components. After application of the CCVR during 5 weeks the following characteristics (mean ± S.D.) with respect to the *release rate* could be established for both components:

Release rate of ENG and EE

Etonogestrel

	1 week	2 week	3 week	4 week	5 week
Conc. (ng/mL)	1.57 ± 0.41	1.47 ± 0.36	1.37 ± 0.32	1.27 ± 0.31	1.17 ± 0.31
In vitro RR (µg/day)	122	107	97	89	82
Abs. Rate* (µg/day)	122 ± 19	115 ± 16	107 ± 14	101 ± 12	93 ± 11

Release rate of ENG and EE

Ethinylestradiol

	1 week	2 week	3 week	4 week	5 week
Conc. (pg/mL)	19.1 ± 4.4	18.3 ± 4.3	17.6 ± 4.3	16.8 ± 4.6	16.1 ± 5.1
In vitro RR (µg/day)	14.3	13.3	12.6	11.9	11.8
Abs. Rate* (µg/day)	8.55 ± 2.50	8.38 ± 2.38	8.21 ± 2.29	8.03 ± 2.22	7.86 ± 2.19

* Absorption rate

Individual regression lines fitted to the ENG indicate a decreasing trend of the mean serum ENG levels of approximately 100 pg/mL per week during weeks 2, 3, 4, and 5 of CCVR use. Individual regression lines fitted to the EE concentrations indicate a decreasing trend of the mean serum EE levels of approximately. 0.77 pg/mL per week during weeks 2, 3, 4, and 5 of CCVR use. A good correlation was found between the *in vivo* and *in vitro* release rates for both components.

Interactions

In an interaction trial the release of ENG and EE from the CCVR was investigated after concomitant application of a spermicide or an anti-mycotic. The table below shows the differences in exposure during several days of ENG and EE after treatments with the spermicide or anti-mycotic, compared with the control period. (as points estimates (P.E.) of the ratios with the corresponding 90% confidence intervals).

	Spermicide treatment		Anti-mycotic treatment	
	ENG	EE	ENG	EE
	P.E and 90% C.I.	P.E and 90% C.I.	P.E and 90% C.I.	P.E and 90% C.I.
AUC_{8-9d}	0.98 (0.89 – 1.08)	0.95 (0.84 - 1.09)	1.03 (0.95 - 1.11)	1.06 (0.96 - 1.18)
AUC_{8-10d}	1.01 (0.91 – 1.11)	1.00 (0.88 - 1.14)	1.07 (0.97 - 1.17)	1.09 (0.97 - 1.21)
AUC_{8-21d}	0.98 (0.90 – 1.07	1.04 (0.99 - 1.08)	1.17 (1.09 - 1.25)	1.16 (1.02 - 1.31)

These results demonstrate that both treatments did not or hardly influence the release of both active compounds from the CCVR. Extrapolation to other oil-based or water based formulations is not directly possible. However, the influence of the vehicle (oil or water) of other vaginal medications may be small.

Influence of removal and storage

Storage after use for 21 days does not influence the in vitro release pattern. So, a similar pattern of release may be expected when a ring is out of the vagina for short periods of time i.e. in the order of three hours. This view is confirmed by results obtained in a pharmacokinetic and pharmacodynamic study. Unintended, temporary removal of NuvaRing for less than 3 hours as indicated in the SPC, will not influence the release characteristics. Similarly, a period of less than 3 hours during which the ring is outside of the vagina will also not affect the serum levels of ENG and EE.

Clinical pharmacodynamics and efficacy trials

Dose-finding

Ethinyl estradiol

Clinical experience with low doses of ethinyl estradiol in monophasic combined oral contraceptives indicated that 20 µg ethinyl estradiol (EE) combined with 150 µg desogestrel (DSG) is sufficient for adequate cycle control. Based upon the reported higher bioavailability of EE after vaginal dosing at the early stages of vaginal ring development, a dose of 15 µg EE was selected for the combined contraceptive vaginal ring.

Etonogestrel

Dose-finding trials were initially performed with prototype vaginal rings, which differed from NuvaRing with respect to their composition as well as their etonogestrel (ENG) content and release rate. The ENG release rate investigated ranged between 75 µg and 150 µg daily, combined with a fixed dose of EE 15 µg. A clear correlation (r^2 = 0.9998) between the in-vitro release rates and the measured ENG serum concentrations was found in these trials. Three different rings were studied for a period of 3 weeks, and compared with Marvelon (oral 30 µg EE + 150 µg DSG). Based on the results of these studies it was decided to select the 120 µg ENG. In order to justify the use of data obtained with prototype Silastic rings for dose selection, ovarian activity of the final design ring was assessed in a comparative study versus Marvelon (30 µg EE + 150 µg DSG). NuvaRing-use resulted in inhibition of ovulation in all subjects for the normal period of use (21

days). Although the assessment of ovarian activity in the Marvelon treatment cycle was only minimal, the ovarian suppression in NuvaRing and Marvelon seemed to be similar. Investigation of extended ring use demonstrated adequate suppression up to at least 28 consecutive days.

Window for removal (treatment-free period) between rings

Clinical investigation suggested three days of use to be sufficient for inhibition of HPO (hypothalamus-pituitary-ovarian)-axis activity. However, the conservative 7-day rule recommended for COCs is maintained, in case contraceptive efficacy is reduced, i.e. a barrier method such as a condom should be used in addition until NuvaRing has been in the vagina for 7 consecutive days

Phase III confirmative study data

The pivotal clinical experience consisted of 2 non-controlled clinical phase III contraception studies, each with the objective to collect at least 10.000 cycles of treatment (study protocols 34219 [EU] and 68003 [VS]). Additionally, four trials were performed to investigate specific safety, which included the effects on lipids, haemostasis, carbohydrate metabolism, adrenal and thyroid function, and local effects. Data on bleeding and contraception of the three metabolic safety studies have been pooled for comparative analysis. In these studies NuvaRing was compared with a levonorgestrel-containing oral contraceptive (150 µg levonorgestrel + 30 µg EE, Microgynon 30).

Dosing schedule

NuvaRing was to remain in the vagina for three weeks, after which it had to be removed. A new ring had to be inserted into the vagina 7 days after removal. The ring could be removed for intercourse if desired, but had to be reinserted within three hours afterwards. The time frame of 3 hours is based on the pharmacokinetic characteristics of both etonogestrel (ENG) and ethinyl estradiol (EE), especially the termination half-lives of approximately 30 hours. It was postulated that serum levels of ENG and EE will hardly be affected as a result of short periods of ring removal, thus it is unlikely that efficacy will be affected by removal of the ring for a period equal or less than 3 hours. No standard back-up advice was given in case of temporary removal, irrespective of the length of this removal. In the metabolic studies, the combined oral contraceptive should be taken for 21 days, followed by a 7-day pill-free period.

Primary efficacy parameters

- Contraceptive efficacy, i.e. prevention of in-treatment pregnancy, evaluated by means of the pregnancy rate or Pearl Index (PI), and overall cumulative probability of in-treatment pregnancy. ITT in-treatment pregnancies have been classified as being per protocol (PP) or non-protocol based on predefined definitions for protocol violations.
- Cycle control
- Safety, as indicated by effects on pharmacological parameters, serious adverse events, local effects and vital signs.

Data collection

In the US study, NuvaRing-use was recorded by subjects using IVRS (interactive voice response system), in the EU study daily diary cards were used. In the metabolic studies, NuvaRing-use and bleeding pattern was recorded by diary card.

Demographics
The included women were educated, predominantly Caucasian, with a mean age of 28 years, a mean body mass index of 22.8 kg/m^2, who were full-time employed (55.3%), students (18.0%), or part-time employed (15.2%). 52.7% of women were nulliparous and 39.4% were nulligravida. The US and the European study populations were rather similar, except for the number of gravid women and black race. Extensive data on body weight provided indicated no clinically relevant correlation between the plasma levels of ENG and EE and the body weight of a subject using NuvaRing.

Efficacy

Contraception
Contraceptive efficacy is summarised in the next table:

Contraceptive efficacy

Group	Trial	N	Total extent of exposure		In-treatment pregnancies	Pearl-Index estimate	95% CI
			Number of 28-day cycles	Woman years			
ITT[a]	068003	1,177	11,188.1	857.7	15	1.749	0.979 - 2.885
	34219	1,145	12,109.4	928.3	6	0.646	0.237 - 1.407
	Combined	2,322	23,297.6	1,786.0	21	1.176	0.728 - 1.797
PP[b]	068003	966	7,032.5	539.1	5	0.927	0.301 - 2.164
	34219	1,049	9,879.6	757.4	3	0.396	0.082 - 1.158
		2,015	16,912.1	1,296.5	8	0.617	0.266 - 1.216
PP#	Combined	2,017	17,049.0	1,307.0	10	0.765	0.367-1.407

[a] Test for homogeneity of ITT Pearl Indices: P = 0.0522 (95% CI for ratio of Pearl indices equals (0.1175, 1.008).
[b] Test for homogeneity of PP Pearl Indices: P = 0.3983 (95% CI for ratio of Pearl indices equals (0.0663, 2.1952)).

PP#: population included for calculation of method failure. Two additional in-treatment pregnancies were included. See text for details.

The overall cumulative probability of an ITT in-treatment pregnancy after one year of NuvaRing use is estimated to be 1.18% (95% CI: 0.728 – 1.797). The overall cumulative probability of a PP in-treatment pregnancy after one year of NuvaRing use is estimated to be 0.48% (95% CI: 0.15 – 0.81). An additional analysis indicated a lack of correlation between the estimated Pearl Index and the four weight categories included. In addition, the company calculated an overall Pearl Index for "*Method failure*" of 0.765 (95% CI: 0.367 – 1.407). In these calculations two additional in-treatment pregnancies were included in women who were protocol violators but in whom these violations did not lead to an increased risk for pregnancy. No in-treatment pregnancies occurred in the metabolic studies and in

the local effects study. Twenty-seven post-treatment pregnancies occurred in the pivotal studies.

Cycle control
An overview of bleeding parameters considered most indicative for cycle control is presented in the next table.

Parameters of cycle control during the first year of use (pivotal studies)

Parameter	Trial 34219 and 068003 combined	
Incidence of	ITT group, range %	PP group, range %
Breakthrough bleeding-spotting	5.1-7.9	3.5-6.6
Absence of withdrawal bleeding	1.5-2.9	1.0-2.3
Intended bleeding [a]	59.9-68.5	60.0-70.0

[a] Cycle 1-12 only, since Cycle 13 analysis for these parameters would have required post-treatment bleeding data.

Pooled data of secondary parameters on bleeding evaluated in the three small metabolic studies suggested no clear differences between groups, although the incidence of intended bleeding was somewhat higher in the NuvaRing group. The latter was due to the lower incidence of continued withdrawal bleeding/spotting (that portion of the withdrawal bleeding that continued into the ring/tablet period of the next cycle).

Compliance
Compliance to the recommended regimen was assessed on a daily basis by using diary cards or the IVRS. The compliance to the ring regimen was higher in Europe than in the US (mean of 91% versus 80%). Furthermore, temporary removals occurred more often in the US study than in the European study.

Safety
An integrated analysis of safety data has been performed on all studies, excluding the pharmacokinetic and pharmacodynamic studies, because in these studies NuvaRing use deviated from the recommended regimen. For the analysis of serious adverse events and vital signs all data were collected in this analysis. The overall safety analysis included 2501 women exposed to NuvaRing, representing a total of 1869,92 woman years (24392.5 cycles). Additionally, 126 women were exposed to LNG/EE, representing 53.61 woman-years of exposure (699.4 cycles). Exposure by duration and dose is summarised in the next table:

Extent of exposure to study medication (all-subjects-treated group)

Duration (days	pilot-studies + metabolic studies		Metabolic studies	
	CCVR (n=2501)		LNG/EE (n=126)	
	N	%	N	%
0 – 84	378	15.1	10	7.9
85 – 168	237	9.5	110	87.3
169 – 252	236	9.4	6	4.8
253 – 336	121	4.8	-	-
≥ 337	1529	61.1	-	-

Adverse events (AEs)

One woman died in a car accident during the clinical studies. In the pilot-studies, 351 (15.1%) of women discontinued treatment due to an adverse event, which in most cases was judged by the investigators as treatment-related adverse events. In the metabolic and local effects studies, 12 of 121 (9.9%) of women discontinued due to an adverse event which were all considered treatment-related with the exception of one adverse event. In the LNG/EE group 4 of 126 (3.2%) women discontinued due to an AE. Overall, 14.8% discontinued due to an adverse event, of which 12.8% were considered drug-related by the investigator. An overview of most frequently reported adverse events (≥1%) that led to discontinuation is presented in table:

AEs reported as primary reason for discontinuation in ³ 1% of study population

AE description	N=2501 [a]
Device-related problems (e.g. expulsion, coital problems, foreign body feeling)	61 (2.4%)
Headache	31 (1.2%)
Emotional lability	27 (1.1%)
Vaginal discomfort	24 (1.0%)

a: all studies that investigated efficacy

Most frequently reported treatment-associated AEs (≥ 1%) included headache, vaginitis, leukorrhoea, device-related problems, weight increase, and nausea. Adverse events, observed in the comparative metabolic studies, did not indicate clear differences between groups.

In total 21 in-treatment pregnancies occurred in the pivotal studies. Fourteen women continued their pregnancy, whereas six had an induced abortion and one had a spontaneous abortion. Three pregnancy outcomes were available: two healthy boys and one healthy girl. No data regarding lactation were collected in the clinical studies. Animal studies indicated that small amounts of orally administered ENG and/or its metabolites are excreted in the milk of lactating rats.

Specific safety issues

Local safety

In all studies that investigated efficacy (n=2501) 2.4% (61) of the women using NuvaRing discontinued due to device related problems (e.g. expulsion, coital problems, foreign body feeling). Information on cervical cytology was extensive, a cervical smear was performed in 1,981 women during treatment with NuvaRing and in 103 women during treatment with LNG/EE. Cervical smears, microbiological examinations, and colposcopy did not indicate negative effects on a local level. Effects of NuvaRing on the endometrium were evaluated by vaginal ultrasound measurements of endometrial thickness, see the discussion under pharmacodynamics. A study is ongoing evaluating the effects of NuvaRing on the endometrium.

Haemostasis

Effects on haemostasis have been evaluated during and after six cycles of NuvaRing use in an comparative study versus oral LNG 150 µg/EE 30 µg. In addition to conventional parameters, a number of new assays have been introduced. These assays detect markers that were generated in the proteolytic process of the

thrombin-generating or fibrinolytic cascade and, in contrast to the more conventional parameters are considered to reflect the 'in vivo' haemostatic activity. Therefore, they may be more predictive of a prethrombotic state than the conventional parameters. These concerned the procoagulation parameters prothrombin fragment 1 and 2 and the thrombin-antithrombin III complex. These parameters are indicative of thrombin generation, and the profibrinolysis parameter plasmin-antiplasmin complex and the fibrin turnover parameters such as D-mer and fibrinogen degradation products as markers of the fibrinolytic cascade. The results at six months are presented in the next table:

Haemostatic parameters, 6 month results

Parameter	**CCVR**	**LNG/EE**
	Median % change (n=38)	**Median % change (n=41)**
Procoagulation:		
Fibrinogen (g/L)	24.5	15.4
Factor VII activity	8.8	-14.7
Prothrombin fragments 1+2 (nmol/l)	39.7	35.2
Thrombin-antithrombin (TAT)(µg/l)	26.7	0.0
Anticoagulation:		
Antithrombin III (%)	0.9	-1.1
Protein C (%)	14.2	6.5
Protein S (%)	0.5	6.7
Profibrinolysis:		
Plasminogen (%)	16.9	26.5
Tissue- plasminogen activator (t-PA) (ng/ml)	-35.8	-46.8
Plasmin-anti-plasmin (PAP) complex (µg/ml)	61.7	35.4
Antifibrinolysis:		
Plasminogen Activator inhibitor-1 antigen (PAI-1Ag)(ng/ml)	-47.2	-59.3
Fibrin turnover:		
D-Dimer	46.8	61.8
Fibrinogen degradation products (FDP) (mg/l)	1.2	30.4

Effects on lipid metabolism

The results of a comparative study versus LNG 150 µg/30 µg EE indicated a decrease in HDL-, HDL_2-, and HDL_3- cholesterol levels from baseline in the LNG/EE group. In the NuvaRing group, HDL was unchanged, HDL_2-C was increased, and HDL_3-C was decreased. As expected, triglycerides increased in both groups.

SHBG, CBG

The synthesis of SHBG and CBG by the liver is known to be influenced by estrogens. Therefore, effects on these carrier proteins were evaluated in an open label comparative study versus oral LNG/EE. In the NuvaRing group a higher increase in SHBG was noted, whereas the increase in CBG was more pronounced in the LNG/EE group.

Effects on carbohydrate metabolism

OCs are known to affect carbohydrate metabolism, resulting in a decrease in glucose tolerance and an increase in insulin resistance. The effects on carbohydrate parameters seen in the NuvaRing group were not statistically significantly different from the effects seen in the LNG/EE group.

Discussion on clinical trial results and evaluation criteria

Contraceptive efficacy
The contraceptive efficacy of NuvaRing was analysed on the basis of two large non-comparative studies, which both had a duration of 13 cycles.
In view of the methodology, the requirements of the Note for Guidance on clinical investigation of steroid contraceptives in women regarding efficacy for a new contraceptive method (CPMP /EWP/519/98, revision 2000) were considered fulfilled:

- The calculation of the Pearl Index for method failure was based on reliable methods for recording of compliance: the US study used electronic diaries and the European study used daily diary cards.
- The number of women and of cycles investigated, and the duration of investigation was sufficient.
- The difference between the point estimate (overall Pearl Index) and the upper limit of the 95% confidence interval did not exceed 1.
- Data on demography did not indicate heterogeneity of fertility for which separate estimates of the Pearl Index should be presented.

Based on 23,297.6 cycles in the intent-to-treat- analysis, an overall Pearl Index for "*typical use" (method + patient failure)* of 1.176 (95% CI: 0.728 – 1.797) is calculated. The Per Protocol analysis, based on cycles in which no significant protocol violation had occurred ("perfect users"), showed a Pearl Index of 0.617 (95% CI: 0.266 – 1.216). In addition to the Per protocol analysis, the company has calculated an overall Pearl Index for *"method failure"* of 0.765 (95% CI: 0.367 – 1.407) based on 17,049.0 cycles.

The combined Pearl Indices were higher than generally observed for oral monophasic combined contraceptives. No comparative contraception study versus an oral combined contraceptive was performed. According to the Note for Guidance on clinical investigation of steroid contraceptives this is not required for products that consistently inhibit ovulation when the Pearl Index is less than 1. This higher overall Pearl Index was in particular due to the higher pregnancy rate in the US-study in comparison with the EU-study. Pharmacodynamic data indicated that inhibition of ovulation and the degree of suppression of ovarian function is in the same range as observed for the comparator (Marvelon). An explanation for the difference should therefore be found elsewhere.

Differences between European and USA study
Especially differences in temporary removals and compliance may have contributed to the observed differences in efficacy between the EU and US study. Further to this, the liberal advice of no back-up in case of temporary removals is a factor of some importance.

- Compliance to the recommended regimen was about 80% in the US study, whereas this percentage was 91% in the European study. Temporary removals did not occur in 75% of women in the US study, whereas this percentage was almost 90% in the European study. There were no differences between the US and EU study for temporary ring removals for a period less than 3 hours. Prolonged temporary removals ,defined as 4-12 hours and 13-24 hours, however appeared to have occurred more frequently in the US study. Apart from this, a higher frequency of prolonged ring-free periods was noted in the US study.

- The advice given in the clinical studies entailed no back-up advice in case of temporary removal, irrespective of the length of this removal. In case subjects questioned their temporary ring removal, the individual investigators were allowed to advise subjects to use additional barrier methods according to their own judgement.
- Calculation of the relation between several risk factors and compliance to NuvaRing revealed the presence of similar risk factors as identified in the literature for COC use. Analysis of data on this point suggested differences in two risk factors for lack of compliance: the percentage of starters and of non-Caucasian women was higher in the US study than in the EU study.

The dose regimen currently recommended in the SPC is much stricter than the recommendations used in the clinical studies, as the instruction for use does not allow temporary removal. Although the effect on efficacy of this stricter dose regimen was not clinically established, this will further improve efficacy.

Cycle control

Information regarding cycle control was adequately collected by daily patient diaries. Analysis of the bleeding pattern was based on the 'cycle' concept, which aims at 'no bleeding' during a ring-period and withdrawal bleeding during a ring-free period. In the combined data of the pivotal studies, the incidence of this intended bleeding pattern varied between 59.9 to 68.5%. Breakthrough bleeding and spotting varied between 5.1-7.9%, and absence of withdrawal bleeding (amenorrhoea) between 1.5 to 2.9% of cycles. A comparable cycle control for NuvaRing was observed in the metabolic studies. Data of the three open comparative metabolic studies versus an oral contraceptive containing 30 µg ethinyl estradiol and 150 µg levonorgestrel was pooled. However, the higher amount of ethinylestradiol (30 µg) and a different progestogen are less suitable for comparison. The pooled data did not indicate clear differences in bleeding pattern, although the incidence of intended bleeding was higher in the NuvaRing group than observed in the LNG/EE group. This difference could be explained by the greater portion of withdrawal bleeding that continued into the tablet period of the next cycle in the EE/LNG group. The mean number of bleeding/spotting days in withdrawal bleeding was comparable between groups.

Safety profile

The adverse event pattern of NuvaRing observed in the pivotal studies indicated a safety profile comparable with that known from oral combined contraceptives, except for vaginitis and device-related problems. Information of pooled data from the comparative metabolic studies is pointing out in the same direction.

Three of all 2501 NuvaRing-treated women experienced a thromboembolic event, which all were assessed as drug-related. These cases included a deep vein thrombosis (DVT) in the leg of a woman who had used NuvaRing for only 8 days, a thrombophlebitis, and a superficial thrombophlebitis.

Effects of NuvaRing on haemostasis, evaluated in an open, randomised comparative study with LNG 150 µg/30 µg EE indicated some differences between treatment groups. The clinical relevance of these differences is unknown, as none of these is considered a validated surrogate end point in the risk of venous thrombosis. Epidemiological investigations have indicated that the increased risk

for venous thrombo-embolic disorders is up to 2 times higher in women using third generation COCs (containing desogestrel or gestodene), than in women using second generation COC's (containing levonorgestrel). Up to now, a definite biological explanation of these observations is lacking.

The differences in VTE risk between COCs observed in the epidemiological studies only concern the monophasic COCs containing a standard dose of ethinyl estradiol (with most of the data pertaining to COCs with 30 µg ethinyl estradiol) combined with desogestrel, gestodene or levonorgestrel. At the time of approval, the conclusion was that for COCs with lower doses of ethinyl estradiol or with other progestagens the data were not sufficient presently to permit firm conclusions. The CPMP at that time recommended the inclusion of the following general warning in the SPCs of all COCs except COCs containing 30 µg or more ethinyl estradiol and desogestrel or gestodene or those containing <50 µg ethinyl estradiol with levonorgestrel:

"Use of any combined oral contraceptive (COC) carries an increased risk of venous thromboembolism (VTE) compared with no use. This increased risk is less than the risk of VTE associated with pregnancy, which is estimated as 60 per 100.000 women. VTE is fatal in 1% - 2 % of cases. It is not known how "*name of the product*" influences the risk of VTE compared with other COCs."

In case of NuvaRing, pharmacokinetic data indicated the average plasma level of ethinyl estradiol to be lower than observed during treatment with Marvelon that contains 30 µg of ethinyl estradiol. It was therefore considered appropriate to include this general warning in the SPC. Apart from this specific statement, the SPC of NuvaRing contains the same list of contra-indications and warnings related to venous thrombo-embolic disorders that are present in SPCs of COCs recently approved after Mutual Recognition Procedures.

The Medicines Evaluation Board did not accept an additional claim of a better cycle control with NuvaRing in comparison with a combined oral contraceptive containing 150 µg levonorgestrel and 30 µg ethinyl estradiol. The pooled data on bleeding control were considered insufficient documentation in support of this claim. The relevance of the differences observed, especially the issue of continued withdrawal bleeding, was doubted.

OVERALL CONCLUSION ON QUALITY, EFFICACY, SAFETY AND BENEFIT/RISK ASSESSMENT

Quality

NuvaRing can be produced with consistent, sufficient quality**.** The shelf-life is 2 years at 2-8°C in the pharmacy, followed by 4 months stored below 30°C at the users'.

Preclinical pharmacology and toxicology

Within the limitations of the toxicology program no special hazard was revealed that would cause the efficacy/safety balance to be unfavourable. The safety profile of NuvaRing is largely based on the extensive human experience with other etonogestrel or desogestrel and ethinylestradiol containing contraceptives.

Clinical efficacy and safety
Overall, the clinical documentation for the hormonal contraceptive NuvaRing was considered appropriate. The clinical dossier met the requirements as recommended in the CPMP 'Note for Guidance on clinical investigation of steroid contraceptives in women' (CPMP/EWP/519/98)".

Benefit/risk assessment
The clinical data led to the conclusion that the risk/benefit ratio for NuvaRing in the requested indication is positive. The presented efficacy in contraception appeared somewhat less than generally observed for oral combined contraceptives. This was due to a higher pregnancy rate in one study, performed in the USA. Differences in temporary removals and compliance together with the liberal advice of no back-up in case of temporary removals, were likely to have contributed to the differences in efficacy between the EU and US study. This was further supported by the Pearl Index for method failure of the European study, which figure was within the range of that noted for oral combined monophasic contraceptives. The instructions for use in the SPC are stricter than the recommendations used in the clinical studies. These instructions do not allow temporary removals.

Regarding safety, the adverse event pattern was not clearly different from that known for oral combined hormonal contraceptives, except for device-related problems. No conclusions can be drawn regarding relative risks for rare events, such as venous thrombosis. Device-related problems are considered a disadvantage. The nature of local problems did not indicate that vaginal administration introduces a significant hazard, although local problems were the most frequent reason for discontinuation. In conclusion, NuvaRing is considered an alternative for women who have problems with compliance to oral contraception with the additional advantage that gastrointestinal disturbance, which may affect contraceptive efficacy, is avoided. However, comparison with other non-oral hormonal alternatives is lacking. Additionally, any clinical advantage of an absence of daily peak concentrations of estrogens and progestogens, in terms of a more favourable adverse event pattern, remains to be established.

The SPC is adapted to the latest European opinions on the use of hormonal combined contraception

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