11.7mg etonogestrel / 2.7mg ethinylestradiol vaginal ring (NuvaRing®) No. (502/08) Schering-Plough

05 September 2008 *(Issued January 2009)*

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

Etonogestrel / ethinylestradiol vaginal ring (NuvaRing®) is not recommended for use within NHS Scotland for contraception.

Results from two randomised phase III clinical studies indicate that the contraceptive efficacy of NuvaRing® is similar to that of two combined oral contraceptives. NuvaRing® produces good cycle control and is associated with high user acceptability. The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Contraception.

Dosing information

Once inserted, NuvaRing should be left in the vagina continuously for 3 weeks and then removed on the same day of the week as the ring was inserted. After a ring-free interval of one week a new ring should be inserted.

Product availability date

12 January 2009.

Summary of evidence on comparative efficacy

NuvaRing is a combined contraceptive vaginal ring designed to release both a progestogen (etonogestrel 0.120mg/24 hours)) and an oestrogen (ethinylestradiol 0.015mg/24 hours) at almost constant release rates for a period of three consecutive weeks. There is then a one week ring-free period to initiate withdrawal bleeding before a new ring is inserted for the next three weeks. The rate of release of ethinyloestradiol is lower than from a transdermal patch Evra® (with an approximate release rate per 24 hours of ethinyloestradiol 0.02mg and norelgestromin 0.15mg) and, since Evra is classified as a low-dose contraceptive, it is probable that this classification will be also be applied to Nuvaring.

Vaginal bleeding characteristics of NuvaRing were evaluated in two open-label, randomised, group-comparative, multi-centre phase III clinical studies, in comparison with the combined oral contraceptives (COCs) Microgynon 30® (containing 150 micrograms levonorgestrel and 30 micrograms ethinylestradiol) and Yasmin® (containing 3mg drospirenone and 30 micrograms ethinylestradiol). The duration of treatment was up to 13 cycles of 28 days, each cycle having a 21-day treatment period followed by a seven-day ring/pill free period. The studies included women at least 18 years of age who were at risk of pregnancy and asking for contraception, with a body mass index ≥18 and ≤29kg/m^2 and a menstrual cycle with a usual length of between 24 and 35 days and an intra-individual variation of not more than ±3 days.

The primary objective of these studies was to demonstrate superiority of the vaginal bleeding characteristics of NuvaRing when compared to the respective oral contraceptive. Diary cards were used for daily documentation of vaginal bleeding patterns and if present, vaginal bleeding was recorded as spotting (requiring one pad/tampon per day or no sanitary protection at all) or bleeding (requiring two or more pads/tampons per day). A bleeding/spotting episode (the primary outcome) was recorded when bleeding or spotting was entered on the Diary Card on one or more consecutive days. Due to the different starting procedures for NuvaRing and the oral contraceptives, the bleeding patterns for cycle 1 were not comparable and the primary analyses were performed on cycles 2 to 13 in each study. Superiority was claimed if there was a statistically significant difference in favour of NuvaRing during any one of the cycles assessed. Correction for multiplicity was applied to the primary outcome but not to other exploratory bleeding parameters.

The secondary objectives were to assess contraceptive efficacy, safety and compliance of NuvaRing versus the respective oral contraceptive. Contraceptive efficacy was determined by the occurrence of in-treatment pregnancies, which was reported as the Pearl Index (PI), the expected number of in-treatment pregnancies per 100 woman years of exposure and its

95% confidence Interval (CI). An additional primary objective in one study was to demonstrate non-inferiority of the effect of NuvaRing compared to Yasmin on body weight.

In the Microgynon 30 study, the Intention-to-Treat (ITT) group consisted of 1,030 randomised and treated subjects (512 in the NuvaRing group and 518 in the Microgynon 30 group). In the Yasmin study, the ITT population consisted of 983 randomised and treated subjects (499 in the NuvaRing group and 484 in the Yasmin group). There were no notable differences between the two groups in demographics or vital signs at screening in either study.

In the Microgynon 30 study, the incidences of breakthrough bleeding-spotting ranged over cycles 2 to 13 from 2.0% to 6.4% in the NuvaRing group and from 3.5% to 13% in the Microgynon 30 group. For all 13 cycles the incidence of breakthrough bleeding-spotting in the NuvaRing group was lower than in the Microgynon 30 group. In total, 10 in-treatment pregnancies were reported in the Microgynon 30 study, five in each treatment group. The estimated PIs for the ITT group of 1.226 (95% CI: 0.3980 to 2.8602) for the NuvaRing group and 1.194 (95% CI: 0.3878 to 2.7870) for the Microgynon 30 group were not statistically different. Compliance with the recommended regimen was high in both treatment groups.

In the Yasmin study, the incidence of breakthrough bleeding-spotting varied over cycles 2 to 13 from 3.6% to 6.2% in the NuvaRing group and from 4.7% to 10% in the Yasmin group. No statistically different treatment effects were found for the primary analysis, thus the superiority claim for NuvaRing over Yasmin with respect to the occurrence of breakthrough bleeding-spotting during cycles 2 to 13 was not demonstrated. The incidence of intended bleeding was statistically higher in the NuvaRing group for each of the cycles 1 to 12, occurring in 55% to 68% of subjects in the NuvaRing group and 36% to 57% of subjects in the Yasmin group. In total, five in-treatment pregnancies were reported, one in the NuvaRing group and four in the Yasmin group. The estimated PIs for the ITT group of 0.245 (95% CI: 0.0062 to 1.363) for the NuvaRing group and 0.988 (95% CI: 0.2692 to 2.53) for the Yasmin group were not statistically different. Weight neutrality of NuvaRing was demonstrated with a mean body weight change from baseline of 0.37kg at last measurement (two-sided 95% CI: 0.10 to 0.64). The estimated mean change from baseline in body weight at last measurement in the ITT group was 0.38kg (two-sided 95% CI: 0.01 to 0.76) lower in the Yasmin group than in the NuvaRing group. Non-inferiority with respect to body weight change from baseline was not demonstrated for NuvaRing.

Data were combined for 1011 subjects in the Nuvaring groups in the comparative studies against Microgynon 30 (521 subjects) and Yasmin (484 subjects). The rates of discontinuation due to in-treatment pregnancy were low (0.3% in the NuvaRing group, 0.8% in the Microgynon 30 group and 0.8% in the Yasmin group) as was unacceptable vaginal bleeding (0.9% in the NuvaRing group, 1.4% in the Microgynon 30 group and 0.6% in the Yasmin group).

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

In the combined analysis of the comparative studies, adverse events (AEs) reported for NuvaRing that may be attributable to the vaginal route of administration included device related problems and vaginitis.

Two cases of deep vein thrombosis in the NuvaRing group, one case of hypertension in the Microgynon 30 group and one case each of abdominal pain and cholelithiasis in the Yasmin

group were considered by the investigator or the submitting company to be possibly, probably or definitely drug-related serious adverse events. The Summary of Product Characteristics (SPC) for NuvaRing states that "it is not known how NuvaRing influences the risk of vascular thromboembolism compared with other combined hormonal contraceptives" cfd. Data from one relatively small multicentre study indicated that NuvaRing does not adversely affect endometrial histology (non-comparative group) or bone mineral density (when compared with a non-hormonal medicated intrauterine device).

In the large comparative studies previously discussed, the overall discontinuation rate was 29% in the NuvaRing group, 29% in the Microgynon 30 group and 25% in the Yasmin group. Discontinuation was mainly due to adverse or serious adverse events, loss to follow-up and other unspecified reasons.

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

The submitting company suggests that NuvaRing is expected to be prescribed to women who might otherwise be prescribed the combined hormonal contraceptive patch, Evra or a COC. Whilst this submission considers comparative clinical data against two COCs, there are no clinical studies comparing NuvaRing and Evra. An indirect comparison of the efficacy and safety of Evra and NuvaRing was undertaken. This indirect comparison utilised a clinical study of Evra against the COC, Triphasil® (triphasic levonorgestrel 50, 75 then 125 micrograms, ethinylestradiol 30, 40 then 30micrograms followed by 7 placebo tablets), which is equivalent to Logynon ED® or Trinordiol® plus 7 inactive tablets. The comparative efficacy data for NuvaRing against Microgynon 30 and Yasmin discussed earlier were used, along with a composite of data from three smaller studies comparing NuvaRing with Microgynon 30. The analysis indicated a 19% lower success rate with NuvaRing than with Evra. Of note, there were inconsistencies in duration between studies, and the number of Caucasian subjects in the Evra comparative study was less than in the other studies, possibly reflecting the fact that the Evra comparative study was conducted in the USA/Canada whereas the other studies were predominantly conducted in Europe. The Evra study was not designed to detect differences in contraceptive efficacy and there was a slight imbalance in the percentage of participants who withdrew or were lost to follow-up (30% in the Evra group and 24% in the Triphasil group). Whilst the results of the Evra study demonstrated a numerically lower overall failure rate for the patch than the oral contraceptive, the authors state that this may have been due to better compliance with the once-weekly dosing regimen of the patch versus daily dosing for the oral contraceptive. Further non-comparative data were included in the analysis used in the economic case such that the results of this analysis were substantially different. Hence, true differences in contraceptive efficacy could not be confirmed.

A recent Cochrane review concluded that contraception effectiveness rates for the patch, vaginal ring and combined oral contraceptives were similar.

Compliance was measured in the study comparing NuvaRing with Microgynon 30 and, although the measures used differed slightly for intravaginal and oral administration, compliance was high in both groups. There are insufficient data to demonstrate improved compliance with the intravaginal device compared with COCs.

The submitting company suggests that NuvaRing provides a useful alternative route of administration for contraceptive hormones when compared with the daily dosing of a COC or the weekly application of a hormonal patch. However, the SPC for NuvaRing indicates that

its insertion/removal should be undertaken according to a strict schedule to ensure that contraceptive efficacy and cycle control is not compromised.

A user acceptability questionnaire carried out as part of the comparative study against Yasmin demonstrated that the majority of subjects did not have any problems with insertion (86%) or removal (89%) of NuvaRing. Fifty-eight percent of subjects commented that they did not feel the ring during intercourse. The majority of subjects in each group were satisfied/very satisfied with the contraceptive method that they used during the clinical study (84% in the NuvaRing group versus 87% in the Yasmin group).

Summary of comparative health economic evidence

The manufacturer presented a cost-effectiveness analysis of the etonogestrel/ethinylestradiol vaginal ring in two comparisons: first with the combined oral contraceptive (COC) pill and second, with the transdermal patch, Evra, in women seeking short and medium-term contraception. The analysis was presented as a decision tree model, with clinical data derived from an indirect comparison of the three treatments. In the model, it was assumed that women discontinuing their initial contraceptive method reverted to an 'average method' of contraception. This average method of contraception had an efficacy rate based on a weighted average of the efficacies of all alternative contraceptive methods. Resource use data for the management of pregnancies was based on a series of assumptions that were tested in a sensitivity analysis.

The time horizon was one year (including the costs of any pregnancies occurring during that year). On this basis, the ring cost an additional £68 per woman compared to the COC pill and reduced the risk of pregnancy by 0.0065 (i.e. by 0.65% in absolute terms). The additional cost per unintended pregnancy averted was £10,552. Compared to the patch, the ring cost an additional £33 per woman and reduced the rate of unintended pregnancy by 0.0032 (0.32% in absolute terms), giving an additional cost of £10,418 per pregnancy averted. The sensitivity analysis was helpful in identifying efficacy as the key variable.

The design of the economic study was adequate, although it should be noted that the niche place in therapy proposed (when the COC pill has been tried or rejected) is narrower than the licensed indication. This called into question the relevance of one of the two comparisons made (i.e. with the COC pill). The comparison with the patch seems more relevant. The manufacturer also proposed a role for the ring following a trial of the patch, but no economic analysis was provided to support this.

The main problems in estimating the benefits relate to the indirect comparison carried out. It was unclear:

- How studies were selected for inclusion – the manufacturer provided further information on this point but it was unclear why the recent Cochrane review of the same question appeared to include more trials
- A lack of information on how the indirect comparison was carried out e.g. how data were combined and whether the women studied were comparable across the trials
- Whether the women recruited reflected the niche role proposed by the manufacturer (following COC use)
- Why point estimates of efficacy for the patch and the ring were used in the economic model when the confidence intervals seem to overlap

The resource use and costs were based on a series of assumptions that were difficult to validate. However, sensitivity analyses suggested these were generally not the critical drivers of the results.

In conclusion, the manufacturer's estimates established that of the three forms of contraception considered the ring is the most expensive. However, the manufacturer provided no robust data to show that there was any additional effectiveness to justify this increased cost. On this basis, the economic case has not been demonstrated to an adequate standard.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

Faculty of Sexual and Reproductive Health Care (Royal College of Obstetricians and Gynaecologists) has published new product reviews on Evra (October 2003) and Cerazette (April 2003) and method specific guidance on the first prescribing of a COC (January 2007), which states that a monophasic COC containing 30 micrograms of ethinylestradiol with norethisterone or levonorgestrel is a suitable first pill.

Additional information: previous SMC advice

Following a full submission, SMC published advice in March 2003: Yasmin is not recommended for use within NHS Scotland as an oral contraceptive. There is no evidence that Yasmin, a new combined oral contraceptive (COC) pill has effects superior to other standard strength COCs on acne, pre-menstrual symptoms or well-being. A statistically significant favourable weight change of 0.3 to 0.7kg compared to a standard strength COC (over a period of 26 cycles) comes at a substantially increased cost. There is no evidence that patients who discontinue other COCs because of weight gain tolerate Yasmin any better. Yasmin is substantially more expensive than competitor products and provides little additional benefits for this additional cost.

Following a full submission, SMC published advice in September 2003: Evra is recommended for restricted use within NHS Scotland as a female contraceptive. Norelgestromin/ethinylestradiol (Evra) patches have efficacy and an adverse-effect profile similar to combined oral contraceptives (COCs). There is some evidence of improved overall compliance with this preparation compared with COCs. It is more expensive than these oral contraceptives. Nevertheless, it is concluded that this preparation may be of benefit in the group of women who have demonstrated, or are deemed to be at, substantial risk of poor compliance with COCs. Use of Evra should be restricted to this group of people.

Additional information: comparators

Whilst an array of contraceptive agents and devices are available, the main comparators to NuvaRing are the COCs such as Yasmin and Microgynon 30 and the combined hormonal contraceptive patch, Evra.

Cost of relevant comparators

Drug	Dose regimen	Cost per cycle (£)	Cost per year* (£)
NuvaRing	**One ring inserted for 21 days followed by a ring-free interval of one week before next ring insertion**	**9.00**	**117**
Evra	One patch applied on day 1 of each cycle replaced by a new patch on day 8 and day 15, followed by a patch-free week starting on day 22 of each cycle	5.42	70
Yasmin	One tablet daily for 21 consecutive days followed by a tablet-free interval of one week before starting next pack of tablets	4.90	64
Microgynon 30	One tablet daily for 21 consecutive days followed by a tablet-free interval of one week before starting next pack of tablets	1.00	13

* 13 cycles included per year. Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 25th June 2008.

Additional information: budget impact

*Other data were also assessed but remain commercially confidential.**

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 22 August 2008.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:* <http://www.scottishmedicines.org.uk/>

The undernoted references were supplied with the submission.

Oddsson K, Leifels-Fischer B, Wiel-Masson D et al. Superior cycle control with a contraceptive vaginal ring compared with an oral contraceptive containing 30 micrograms ethinylestradiol and 150 micrograms levonorgestrel: A randomized trial. Human Reproduction 2005;20(2):557-562.

Oddsson K, Leifels-Fischer B, de Melo NR et al. Efficacy and safety of a contraceptive vaginal ring (NuvaRing) compared with a combined oral contraceptive: A 1-year randomized trial. Contraception 2005;71(3):176-182.

Milsom I, Lete I, Bjertnaes A et al. Effects on cycle control and bodyweight of the combined contraceptive ring, NuvaRing, versus an oral contraceptive containing 30 micrograms ethinyl estradiol and 3mg drospirenone. Human Reproduction 2006;21(9):2304-2311.