Scottish Medicines Consortium

Resubmission

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

04 September 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 resubmission

etonogestrel / ethinylestradiol vaginal ring (NuvaRing®) is accepted 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 user acceptability. Cost-effectiveness has been demonstrated in women who chose to discontinue oral contraceptives. Other non-oral contraceptives are available at lower cost.

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 which when inserted into the vagina releases, at a constant rate over a three week period, etonogestrel 0.120mg/24 hours and ethinylestradiol 0.015mg/24 hours. After three weeks the ring is removed for a one-week ring-free period to initiate withdrawal bleeding to complete the cycle.

The submitting company requested that the Scottish Medicines Consortium consider the use of this product in a sub-set of the licensed indication, for those patients who are dissatisfied with the oral contraceptive pill. NuvaRing would add another second-line option to the other alternatives available.

The efficacy of NuvaRing to prevent unintended pregnancy was determined by the number of in-treatment pregnancies, 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). Contraceptive efficacy was measured as the primary study outcome in two open-label non comparative phase lll studies in a total of 2322 women over 13 cycles (equivalent to 1786 woman years of NuvaRing use), which resulted in a total of 21 in-treatment pregnancies, and a PI of 1.18 (95% CI: 0.73 to 1.80).

Having established the contraceptive efficacy of NuvaRing, two open-label, randomised, comparative, phase III studies in a total of 2013 women, evaluated the vaginal bleeding characteristics of NuvaRing, compared with the combined oral contraceptives (COCs) Microgynon 30 (containing levonorgestrel 150 micrograms and ethinylestradiol 30 micrograms) and Yasmin (containing drospirenone 3mg and ethinylestradiol 30 micrograms). 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 ≥18 years requesting contraception, with a body mass index ≥18 and ≤29kg/m^2 and a menstrual cycle of between 24 and 35 days.

The primary objective was to demonstrate superiority of the vaginal bleeding characteristics of NuvaRing over the combined oral contraceptive. Vaginal bleeding patterns were recorded daily and if present, were reported as a spotting or bleeding episode. 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.

The secondary objectives were to assess contraceptive efficacy (determined by the number of in-treatment pregnancies, reported as the PI), safety and compliance of NuvaRing versus

the oral contraceptive. 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 women (512 in the NuvaRing group and 518 in the Microgynon 30 group). In the Yasmin study, the ITT population consisted of 983 women (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 over cycles 2 to 13 ranged from 2.0% to 6.4% in the NuvaRing group and from 3.5% to 13% in the Microgynon 30 group. In all 13 cycles in the NuvaRing group the incidence of breakthrough bleeding-spotting was lower. Ten in-treatment pregnancies were reported, five in each treatment group. The estimated PIs were 1.23 (95% CI: 0.40 to 2.86) for the NuvaRing group and 1.19 (95% CI: 0.39 to 2.79) for the Microgynon 30 group. Compliance with the recommended regimen was high in both treatment groups.

In the Yasmin study, the incidence of breakthrough bleeding-spotting over cycles 2 to 13 ranged from 3.6% to 6.2% in the NuvaRing group and from 4.7% to 10% in the Yasmin group, with no significant difference reported in any cycle for the primary analysis. Therefore the superiority of NuvaRing over Yasmin was not demonstrated. The incidence of intended bleeding was significantly higher in the NuvaRing group, 55% to 68% of women compared with 36% to 57% of women 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 of 0.25 (95% CI: 0.006 to 1.36) for the NuvaRing group and 0.99 (95% CI: 0.27 to 2.53) for the Yasmin group were not significantly different. Weight neutrality of NuvaRing was demonstrated with a mean body weight change from baseline of 0.37kg (95% CI: 0.10 to 0.64). The estimated mean change from baseline in body weight was 0.38kg (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 versus Yasmin as the upper limit of the CI was above the pre-specified value of 0.75kg.

Data were combined for 1011 subjects in the NuvaRing groups in the comparative studies against Microgynon 30 (518 women) and Yasmin (484 women). 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

NuvaRing is generally safe and well tolerated. The usual spectrum of adverse events reported for combined hormonal contraceptives were reported in the clinical studies of NuvaRing, including nausea, headache, mood alterations, breast tenderness, weight gain and decreased libido.

In the comparative studies, for the adverse events considered by the investigator to be at least possibly related to study drug (with an incidence of ≥ 1%) the most frequent in all three groups was headache. Several adverse events apparently related to the vaginal route of administration were more frequent in the NuvaRing group (device related problems: 5.6% versus 0% versus 0.4%; vaginitis: 4.3% versus 1.0% versus 2.1% and leucorrhoea; 3.5%

versus 0.2% versus 1.0%), while the incidence of nausea (1.8% versus 4% versus 3.7%) was slightly higher in the Microgynon 30 and Yasmin groups.

The combined hormonal contraceptives have been associated with a slightly increased risk of venous thromboembolism. In the clinical trial programme, two cases of deep vein thrombosis reported in the NuvaRing group, were considered by the investigator to be at least possibly drug-related. 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". 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.

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

Summary of clinical effectiveness issues

The submitting company has requested that the Scottish Medicines Consortium consider the use of this product in a sub-set of the licensed indication, for those patients who are dissatisfied with the oral contraceptive pill. NuvaRing would be another second-line option along with the other alternatives already available, the contraceptive patch, parenteral progesterone-only contraceptives, intra-uterine devices and non-hormonal methods of contraception.

Whilst the submission considers comparative clinical data against two COCs, there are no clinical studies comparing NuvaRing with the other alternative methods of contraception. Therefore an indirect comparison with these other methods was presented. However, as the contraceptive methods included are very disparate (including devices and hormonal, barrier and natural methods), the populations and study durations varied, there are a number of inherent problems with the comparison.

In the direct comparisons with other hormonal methods the number of in-treatment pregnancies in all studies was small and therefore the studies were not large enough to demonstrate any significant differences. In addition the duration of the studies and populations included varied. The reporting of vaginal bleeding patterns on an individual monthly basis has limitations and gives no indication as to whether the bleeding irregularities reported are recurring bleeding episodes in the same women each month or from different women.

A recent Cochrane review concluded that contraception effectiveness rates for the patch, vaginal ring and combined oral contraceptives were similar. However the patch group had better compliance than the COC group, but more side effects, whilst the ring users had fewer adverse events than COC users but more vaginal irritation and discharge, although the incidence of these were relatively low.

Compliance was measured in the studies comparing NuvaRing with Microgynon 30 and with Yasmin. Compliance was high in all groups but there are insufficient data to demonstrate improved compliance with the intravaginal device compared with COC. 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 contraceptive efficacy and cycle control may be compromised if the woman deviates from the recommended regimen. The SPC provides advice to avoid loss of contraceptive efficacy in such circumstances.

Results from a user acceptability questionnaire carried out as part of the comparative study against Yasmin suggested that the majority of women did not have any problems with insertion or removal of NuvaRing. Fifty-eight percent of women commented that they did not feel the ring during intercourse and the majority were satisfied/very satisfied with the contraceptive method.

Clinical experts advised the Scottish Medicines Consortium that NuvaRing presents another useful choice of non-oral contraception for women and may be particularly suitable for women in whom compliance is a problem with the COC.

Summary of comparative health economic evidence

The manufacturer submitted a cost-effectiveness analysis comparing NuvaRing with a weighted average method in women seeking short and medium-term contraception who have chosen to discontinue from oral contraceptives. The weighted average included a number of hormonal methods (contraceptive patch, implant, injectable, intra-uterine device (IUD) and intra-uterine system (IUS)) as well as natural and barrier methods. A decision tree model was used to estimate the costs and benefits of NuvaRing over a one year time horizon. Clinical data on contraceptive failure rates were based on an indirect comparison of NuvaRing with the various methods included in the weighted average of second line treatments. NuvaRing was estimated to have a yearly failure rate of 0.81% compared with 2.41% for the weighted average method. The weighted average cost per pregnancy was estimated to be £2,150 based on the estimated proportions of the different pregnancy outcomes (live birth, abortion, miscarriage or ectopic pregnancy). The ICER for NuvaRing compared with the weighted average method was estimated to be £3,337 per pregnancy avoided based on an increased cost of £53 per woman per year with a reduced risk of pregnancy of 0.01578.

Some weaknesses were identified with the economic analysis:

- The studies used in the indirect comparison had different study designs, different patient populations and included a wide range of contraceptive methods, some of which may not be appropriate such as natural and barrier methods. Based on these studies, the manufacturer conducted a naïve indirect comparison which did not adjust for the differences between the studies. As such, the efficacy estimates from this analysis are uncertain.
- The inclusion of natural and barrier methods lowers the efficacy rate of the weighted average method considerably. When non-hormonal methods were excluded, the analysis showed that NuvaRing would be less costly but also less effective than the weighted average hormonal method over a one year time horizon. As some of the hormonal methods (such as the implant, IUD and IUS) are effective for 3 or 5 years, a longer time horizon is more appropriate in order to justify the higher costs in the first year of use. Extending the time horizon would result in NuvaRing being dominated by the weighted average hormonal method.
- Patients in the studies may not reflect the niche position proposed by the manufacturer i.e. women who have discontinued use of oral contraceptives.

Despite some weaknesses with the economic case, NuvaRing provides an alternative choice of contraception for women at an acceptable cost.

Summary of patient and public involvement

A Patient Interest Group submission was received from the Family Planning Association

Additional information: guidelines and protocols

The Faculty of Sexual and Reproductive Health Care (Royal College of Obstetricians and Gynaecologists) has published new product reviews on Nuvaring (March 2009), 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: comparators

A wide range of contraceptive agents and devices are available and include the COC, the combined hormonal contraceptive patch (Evra®), progesterone only oral contraceptives (desogestrel, etynodiol, norethisterone, levonorgestrel), an implant (Implanon®), an injectable (Depo-Provera), an intra-uterine device (Mirena®) and other intra-uterine devices.

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**	**117**
Mirena®	Inserted into uterine cavity within 7 days of onset of menstruation. Effective for 5 years	-	87[1,3]
Implanon®	One implant inserted within first 5 days of cycle. Effective for 3 years.	-	79[1,2]
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	5.21	68
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
Cerazette®	One tablet daily on day 1 of cycle then continuously	2.95	38
Depo-Provera®	150mg by deep intramuscular injection within first 5 days of cycle every 12 weeks.	2.04	26 [1]
Intra-uterine device	Inserted into the uterine cavity during the first half of cycle	-	8 to 12[1]
Microgynon 30	One tablet daily for 21 consecutive days followed by a tablet-free interval of one week before starting next pack of tablets	0.96	12

Micronor®	One tablet daily on day 1 of cycle then continuously	0.59	8

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 24 June 2009. [1]Excludes the costs of insertion/injection. [2] Cost for up to 3 years . [3] Cost for up to 5 years This list is not exhaustive.

Additional information: budget impact

The manufacturer estimated the net drug budget impact would be £10k in year 1 rising to £45k in year 5 based on 144 patients in year 1 rising to 551 in year 5. The gross drug budget impact was estimated to be £20k in year 1 and £90k in year 5.

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 13 August 2009.

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. The reference shaded grey is additional to those 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.

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