Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

Resubmission

drospirenone/ethinylestradiol, 3mg/30micrograms, film-coated tablets (Yasmin®) SMC No. (23/03)

Bayer Schering Pharma

04 March 2011

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

ADVICE: following a resubmission

drospirenone/ethinylestradiol (Yasmin®) is not recommended for use within NHS Scotland.

Indication under review: oral contraception.

Drospirenone/ethinylestradiol has been shown to have similar contraceptive effectiveness to other combined oral contraceptives in routine use, with no significant differences in adverse event profile.

The manufacturer did not present a sufficiently robust economic case to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

Oral contraception.

Dosing Information

One tablet to be taken orally daily for 21 consecutive days.

Product availability date

April 2002

Summary of evidence on comparative efficacy

The contraceptive effect of drospirenone/ethinylestradiol is largely due to inhibition of ovulation and changes in the endometrium. Drospirenone possesses antiandrogenic and mild antimineralocorticoid properties.

The evidence of comparative efficacy of drospirenone/ethinylestradiol is based on two similar, phase III randomised controlled open-label studies and from a phase IV observational cohort study. In all studies, contraceptive efficacy was reported using the Pearl Index, defined as the number of pregnancies for every 100 women years of contraceptive exposure.

The two phase III, open-label studies randomised women, aged 18 to 35 years, eligible for oral contraception and willing not to use other hormonal contraceptive measures, to drospirenone 3mg/ethinylestradiol 30micrograms, or desogestrel 150 micrograms/ethinylestradiol 30micrograms, taken daily for 21 consecutive days, followed by a seven-day pill-free period. Patients were followed up for 26 cycles in the first study, and 13 cycles in the second study. In addition to the primary outcome of the Pearl Index, the secondary outcome of cycle control was determined by the rates of intermenstrual bleeding in each group.

In the first study, 442 women received treatment with drospirenone/ethinylestradiol and 445 women desogestrel/ethinylestradiol, giving a total exposure of 9563 and 9498 cycles, respectively. The Pearl Index for both groups was 0.41 pregnancies per 100 women years (95% confidence intervals [CI] were not reported). There was no difference in the rates of intermenstrual bleeding events between the two groups, with bleeding occurring in 9.0% of drospirenone/ethinylestradiol cycles and in 8.6% of desogestrel/ethinylestradiol cycles. Bleeding was more likely early in the study, and in the majority of cases was reported as spotting.

In the second study, 1680 women were randomised to drospirenone/ethinylestradiol, and 418 women to desogestrel/ethinylestradiol, giving a total exposure of 18,418 cycles and 4685 cycles for analysis. There were ten pregnancies in the drospirenone/ethinylestradiol group and one pregnancy in the desogestrel/ethinylestradiol group, resulting in Pearl Indices of 0.71/100 and 0.28/100 women years, respectively. The one pregnancy in the desogestrel/ethinylestradiol group was judged to be due to method failure but only one of the ten pregnancies in the drospirenone/ethinylestradiol group was judged to be due to method failure and when co-factors for reduced efficacy of contraception were considered, including missed pills and diarrhoea, the Pearl Indices for drospirenone/ethinylestradiol and desogestrel/ethinylestradiol were 0.07 and

0.28, respectively. There was no significant difference between groups in the rate of intermenstrual bleeding.

The phase IV cohort study followed 58,674 women from across Europe including the UK, who were either first-time users of oral contraception, or existing users switching to a new oral contraceptive. Patients were followed via biannual questionnaires for up to five years, with a mean follow up of 2.4 years. This was primarily a safety study with contraceptive efficacy reported as a secondary outcome. There was a total oral contraceptive exposure of 112,659 women years with 545 unplanned pregnancies being reported giving an overall Pearl Index of 0.48 (95% CI: 0.44 to 0.53). There was no significant difference in contraceptive effectiveness between the different progestogen containing oral contraceptive groups.

Summary of evidence on comparative safety

The overall adverse event profile of drospirenone/ethinylestradiol is similar to other combined oral contraceptives. The rates of serious adverse events reported in the large European cohort study were similar regardless of type of progestogen taken, range 337 to 345 events per 10,000 women years.

The incidence of treatment related adverse events reported by patients in the phase III randomised studies was similar between the two groups. There was no statistical difference in the incidence of premenstrual symptoms, with 18% of patients in the drospirenone/ethinylestradiol group reporting symptoms compared with 20% in the desogestrel/ethinylestradiol group. Patients in the drospirenone/ethinylestradiol group had a consistently lower mean body weight compared to baseline from cycles 1 to 24 (range -0.11 to -0.68kg), whereas patients in the desogestrel/ethinylestradiol group had a lower mean body weight only in cycles 1 to 5, after which the mean body weight was 0.02 to 0.89kg above baseline.

In the second study there were similar reductions in the incidence of acne and seborrhoea from baseline to cycle 13 for both treatment groups. Patients reported mean weight losses compared to baseline in both groups but the degree of weight loss was significantly greater in the drospirenone/ethinylestradiol group; -0.46kg versus -0.19kg.

The primary outcome in the phase IV cohort study was cardiovascular events and the study was powered to demonstrate non-inferiority in venous thromboembolism (VTE) risk of drospirenone-containing oral contraceptives compared with levonorgestrel-containing and other oral contraceptives. Only a small number of VTE events were reported and no difference in the rate of VTE between the different cohorts was observed. The adjusted hazard ratio (HR) of VTE occurrence in the drospirenone/ethinylestradiol cohort was 0.9 (95% CI: 0.6 to 1.4), for levonorgestrel/ethinylestradiol the HR was 1.0 (95% CI: 0.6 to 1.8) and for the other oral contraceptives the HR was 0.8 (95% CI: 0.5 to 1.3). Discontinuation rates showed similar numbers of women within the different cohorts stopped oral contraception or switched to an alternative combined oral contraceptive. Of the women initially prescribed drospirenone/ethinylestradiol, 21% switched to an alternative or stopped oral contraception, compared to 22% of women prescribed levonorgestrel-containing contraception, and 27% of other oral contraceptive users.

The reason for switching to another contraceptive or discontinuation was intolerance or adverse events in 12%, 16%, and 20% of women in each cohort, respectively.

A retrospective observational study from GP practices in the UK examined continuation rates of oral contraceptives over 12 months following initial prescription. Data were obtained from case notes, and discontinuation was defined as the participant's failure to return for another prescription for the same medicine, pregnancy or alternative prescription. In total, 316 women were enrolled in each cohort, and the rate of discontinuation was significantly less in the drospirenone/ethinylestradiol group compared with the comparator cohort after 12 months (63% versus 71%).

In April 2010, the Medicines and Healthcare products Regulatory Agency (MHRA) provided updated advice on the risk of VTE with drospirenone/ethinylestradiol based on recent observational studies. These studies suggested a relative risk of VTE of 1.64 to 1.7 compared to levonorgestrel-containing pills. Due to the limitations of the studies and wide confidence intervals, no firm conclusions could be drawn.

Summary of clinical effectiveness issues

With the exception of emergency hormonal contraception, the Pearl Index is recommended by the European Medicines Agency for measuring the efficacy of hormonal contraceptives. Estimates of the Pearl Index for drospirenone/ethinylestradiol are available from two randomised controlled studies and a phase IV observational cohort study.

There were slight variations in how the effectiveness measure was calculated between the studies. The two randomised controlled studies only included those cycles in which at least 19 pills were taken. In addition one of these studies presented a Pearl Index adjusted for co-factors, including missed pills, diarrhoea and other events. It is not clear how the impact of these co-factors on the outcome was tested but they were judged to have caused nine out of the ten pregnancies recorded. The European cohort study used all cycles in which oral contraception was used regardless of patient compliance. This study was designed to minimise the risk of sources of bias common to cohort studies: recruitment of patients only after the prescription of an oral contraception had been made; a comprehensive program to minimise loss to follow-up; and well-matched control groups. The Pearl Index estimated from the cohort study is likely to be more valid to the Scottish population than the one estimated from the randomised studies.

The European cohort study suggested a small advantage in tolerability for drospirenone/ethinylestradiol over alternative contraceptives in relation to the reported discontinuations due to adverse events. The retrospective GP cohort study also demonstrated a reduced discontinuation rate for drospirenone/ethinylestradiol over 12 months compared with other oral contraceptives.

Summary of comparative health economic evidence

The manufacturer submitted a cost-effectiveness analysis comparing drospirenone/ethinylestradiol with a weighted average of alternative brands of combined oral contraceptives (COCs). A Markov model with a 1-year time horizon was used, with states including first-choice of contraception, second choice (following discontinuation), unintended

pregnancy (UIP) and post-unintended pregnancy. The time horizon was flexible to some extent to capture costs if a UIP occurred towards the end of the 1-year time horizon.

The comparator was the weighted average of alternative brands of COCs, based on Scottish prescribing data for 2010. The second choice of contraception, when women discontinued their first choice, was a weighted average of all contraception methods, based on a survey conducted by the manufacturer in women taking contraception in the UK. Within the model there was no option for women to discontinue their second choice. The key clinical data for each form of contraception were effectiveness rates (Pearl Index, PI) and the discontinuation rate. The manufacturer argued that randomised controlled trials were likely to give unrealistic estimates and that 'real world' clinical studies were to be preferred.

Costs for contraception included medicines, GP consultations and (where appropriate) costs of inserting/removing forms of contraception. Costs of UIP included the cost of a live birth, termination of pregnancy, miscarriage and ectopic pregnancy.

Using the base case assumptions the manufacturer claimed that drospirenone/ethinylestradiol was dominant over the weighted average of alternative COCs since it was cost saving and resulted in fewer UIPs. Drospirenone/ethinylestradiol was estimated to cost £424 overall, including the cost of an unintended pregnancy when it occurred, versus £429 for a first-choice alternative combined oral contraceptive. The unintended pregnancy rate was 0.092 for drospirenone/ethinylestradiol and 0.108 for a first choice alternative combined oral contraceptive. This implies a saving of £5.46 per woman per year and 0.016 fewer unintended pregnancies per woman per year.

Sensitivity analysis showed that this result still held when effectiveness and discontinuation rates were varied through their 95% confidence interval and when UIP costs were changed by +/-30% with the following exceptions:

- comparator COC discontinuation at lower limit of 95% CI resulted in an added £2741 per unintended pregnancy avoided
- drospirenone/ethinylestradiol discontinuation at upper limit of 95% CI resulted in an added cost of £2356 per unintended pregnancy avoided
- UIP cost lowered by 30% resulted in added cost of £245 per pregnancy avoided

In response to questions from SMC the manufacturer provided further analyses that equalised Pearl Index rates across treatments and that considered drospirenone/ethinylestradiol as a final choice of oral contraceptive before non-oral forms were considered. These were considered at SMC but in an additional sensitivity analysis the effect of equalising the discontinuation rates was shown to be £51,408 per pregnancy avoided (based on a difference of £32.13 per year more and 0.001 fewer pregnancies per woman). Given the SMC's concerns about the quality of the clinical studies supporting the difference in discontinuation rates, this raised concern about the cost-effectiveness case

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

Summary of patient and public involvement

A Patient Interest Group submission was received from The Family Planning Association.

Additional information: guidelines and protocols

The Royal College of Obstetricians and Gynaecologists published guidance for "Venous thromboembolism and Hormonal Contraception" in July 2010.

- The relative risk of VTE is increased with all combined hormonal contraceptives (pills, patch, and vaginal ring). Nevertheless, the rarity of VTE in women of reproductive age means the absolute risk remains small.
- The relative risk of VTE increases in the first few months after initiating combined hormonal contraception (CHC). The risk reduces with increasing duration, but remains above background risk until CHC is stopped.

The Faculty of Sexual and Reproductive Healthcare have issued several relevant guidelines; "First prescription of combined oral contraception" in July 2006; "Contraceptive choices for young people" in March 2010; and "Contraception for women aged over 40 years" in July 2010. There was no specific guidance regarding drospirenone/ethinylestradiol, but the guidelines outline the evidence for the safe use of combined hormonal contraception in these age groups, with reference to the UK Medical Eligibility Criteria for combined oral contraception.

NHS Clinical Knowledge Summaries for contraception recommends when offering combined oral contraceptives: first-line options are monophasic preparations containing 30micrograms of oestrogen, and either norethisterone or levonorgestrel. However all combined oral contraceptives can be considered according to patient preference.

Additional information: comparators

Combined oral contraceptives; there are many different preparations available in the UK that are prescribed according to healthcare professional and/or patient preference.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Ethinylestradiol 30 micrograms/ drospirenone 3mg tablet (Yasmin®)	**One tablet to be taken orally daily for 21 consecutive days followed by a seven-day pill-free period each cycle.**	**£64**
Ethinylestradiol 30 micrograms/ desogestrel 150 micrograms tablets (Gedarel® 30/150)	One tablet to be taken orally daily for 21 consecutive days followed by a seven-day pill-free period each cycle	£21
Ethinylestradiol 30 micrograms/ gestodene 75 micrograms tablets (Millinette® 30/75)	One tablet to be taken orally daily for 21 consecutive days followed by a seven-day pill-free period each cycle	£21

Ethinylestradiol 30 micrograms/ norethisterone 1.5mg tablets (Loestrin 30®)	One tablet to be taken orally daily for 21 consecutive days followed by a seven-day pill-free period each cycle	£17
Ethinylestradiol 35 micrograms/ norgestimate 250 micrograms tablets (Cilest®)	One tablet to be taken orally daily for 21 consecutive days followed by a seven-day pill-free period each cycle	£12
Ethinylestradiol 35 micrograms/ norethisterone 1mg tablets (Norimin®)	One tablet to be taken orally daily for 21 consecutive days followed by a seven-day pill-free period each cycle	£10
Mestranol 50 micrograms/ norethisterone 1mg tablets (Norinyl-1®)	One tablet to be taken orally daily for 21 consecutive days followed by a seven-day pill-free period each cycle	£9
Ethinylestradiol 30 micrograms/ levonorgestrel 150 micrograms tablets (Rigevidon®)	One tablet to be taken orally daily for 21 consecutive days followed by a seven-day pill-free period each cycle.	£8
Ethinylestradiol 35 micrograms/ norethisterone 500 micrograms tablets (Ovysmen®)	One tablet to be taken orally daily for 21 consecutive days followed by a seven-day pill-free period each cycle	£6

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 10 January 2011. Costs based on 13 treatment cycles per year

Additional information: budget impact

The manufacturer estimated a net medicines budget impact of £245k in year 1 rising to £1.2m by year 5. Offsetting this increase would be savings on managing unintended pregnancies, estimated at £415k per annum.

However (i) this assumed a difference in the Pearl Index, which has not been proven, and (ii) the calculation is based on the new cohort starting each year. The offset over 5 years was estimated to be £2.1m.

The manufacturer estimated that around 301,000 Scottish women will choose an oral contraceptive in 2011. The budget impact calculation assumed that acceptance by SMC would increase the market share over five years to 5,091 additional women choosing ethinylestradiol/drospirenone in year 1 rising to 25,536 in year 5.

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

References

The undernoted references were supplied with the submission.

Foidart JM, Wuttke W, Bouw GM, Gerlinger C and Heithecker R. A comparative investigation of contraceptive reliability, cycle control and tolerance of two monophasic oral contraceptives containing either drospirenone or desogestrel. Eur J Contracept Reprod Health Care 2000; 5(2):124-134.

Huber J, Foidart JM, Wuttke W et al. Efficacy and tolerability of a monophasic oral contraceptive containing ethinylestradiol and drospirenone. Eur J Contracept Reprod Health Care 2000; 5: 25-34

Dinger JC, Mohner S, Minh TD, Cronin M, Schellschmidt I and Westhoff C. Oral contraceptive effectiveness according to body mass index, weight, age, and other factors. Am J Obstet Gynecol 2009; 201(3):263

Dinger JC, Heinemann LA and Kuhl-Habich D. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation. Contraception 2007; 75(5):344-354.

Mansour D and Lister S. A study to compare continuation rates between Yasmin and existing COCs in UK clinical practice. Poster Presented at the 8th Congress of the European Society of Contraception, Edinburgh. 2004.

**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/*

This assessment is based on data submitted by the applicant company up to and including 15 February 2011.

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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.