

**Tablets containing 1 mg estradiol and 2 mg drospirenone
(Angeliq^o)** **(No: 230/05)**

Schering Health Care Ltd

New product for the indication: prevention of menopausal symptoms

9 December 2005

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

1 mg estradiol/2 mg drospirenone (Angeliq®) is not recommended for use within NHS Scotland as hormone replacement therapy for oestrogen deficiency symptoms in postmenopausal women more than 1 year post-menopause.

It is effective in reducing the frequency of hot flushes and other symptoms of the menopause but comparative data versus other low dose continuous combined treatment are lacking. The cost-effectiveness has not been demonstrated and there are cheaper alternatives.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

**1 mg oestradiol and 2 mg
drospirenone
(Angeliq®)**

Indication

Hormone replacement therapy for oestrogen deficiency symptoms in postmenopausal women more than 1 year post-menopause.

Dosing information

One tablet daily, continuously

UK launch date

June 2005

Comparator medications

Comparators include a variety of estradiol + progestagen preparations, Premique® and tibolone.

Cost of relevant comparators

There is a wide range of preparations offering hormone replacement therapy and licensed for this indication. The following table gives costs for a year's treatment (thirteen 28-day cycles) of preparations, which offer continuous oral treatment with oestradiol 1 mg/day in combination with a progestogen, for Premique® which was a comparator in one trial and for tibolone which was the comparator in the health economic analysis.

| Preparation | Progestogen | Cost per annum |
|---------------------------------|------------------------------------|-----------------------|
| Angeliq ^o | Drospirenone 2 mg | £112 |
| Femoston-conti [®] | Dydrogesterone 5 mg | £88 |
| Indivina ^{®*} | Medroxyprogesterone acetate 2.5 mg | £93 |
| Kliovance [®] | Norethisterone acetate 0.5 mg | £64 |
| Tibolone (Livial [®]) | Not applicable | £140 |
| Premique ^{®+} | Medroxyprogesterone acetate 5 mg | £118 |

* May be titrated up to 2 mg ethinyloestradiol

+ Contains conjugated oestrogens 0.625 mg

Summary of evidence on comparative efficacy

A double-blind randomised placebo-controlled trial was conducted to evaluate the symptomatic efficacy of oestradiol combined with 1 mg, 2 mg or 3 mg drospirenone (drospirenone 1mg/estradiol 1 mg, drospirenone 2 mg/estradiol 1 mg [the licensed formulation] and drospirenone 3 mg/estradiol 1 mg).

The study population consisted of 225 healthy post-menopausal Caucasian women aged 45-65 years who complained of at least five moderate to severe hot flushes per day on at least 7 of the 14 days preceding the study. Patients who met defined criteria for post-menopausal status were admitted if they had an intact uterus and a normal endometrium, or if they had undergone a hysterectomy.

Exclusion criteria included: contraindications for hormone replacement therapy; treatment with anticoagulant medications; use of oral, transdermal or transvaginal hormonal preparations within 6 weeks or long-acting injectable or implanted preparations 6 months preceding the study; a past medical history significant for cardiovascular disease; depression; diabetes mellitus; hypertension; thromboembolic disease; alcohol or drug abuse or other diseases or conditions that could, in the opinion of the investigator, affect study results; participation in another clinical study within 1 month and use of an investigational drug within 3 months prior to the study.

The primary study end-points were the change in frequency and intensity of hot flushes from baseline. For each active treatment, the null hypothesis was that the relative change in the mean number of hot flushes per week from a 2-week pre-treatment period to the average of 3-16 weeks of the treatment period would be larger with drospirenone/estradiol than with placebo. It was planned to test this hypothesis with a one-sided parametric Dunnett test. However, since the distribution of the primary variable differed considerably from a normal distribution, additional non-parametric one-sided Wilcoxon rank sum tests were performed to compare the three active treatments with placebo. For both types of test the hypothesis was tested against a significance level of $\alpha=0.025$ and the one-sided Wilcoxon rank sum exact 'p' value was reported after Bonferroni correction for multiple comparisons.

By week 16, the mean number of hot flushes per week was reduced by 84%-88% in the active treatment groups and by 47% in the placebo group, and the difference was significant by both parametric and non-parametric tests for all groups compared with placebo. The reduction in both moderate and severe hot flushes was significantly more pronounced than that observed for mild hot flushes in the active treatment groups. In the active treatment groups, the mean number of moderate or severe hot flushes per week was reduced from an average of 21.8 to 29.8 at baseline to 1.0-2.0 in week 16. The number of mild hot flushes decreased from 7.4-9.6 (mean per week) at baseline to 1.4-3.7 in week 16.

Secondary variables were not subject to statistical analysis, but the incidence of six other menopausal symptoms was similar at baseline for all groups and at week 16 the reduction in frequency was numerically greater in each of the active treatment groups than with placebo. Frequency of urination was least common in the placebo group at baseline and the reduction was similar to that with drospirenone 2mg/estradiol 1mg.

One open-label trial compared the effect on lipid parameters of drospirenone/estradiol and conjugated oestrogens 0.625 mg/ medroxyprogesterone acetate 5 mg (CEE/MPA, Premique®). As a secondary end-point there was a decrease in all treatment groups in the frequency and intensity of menopausal symptoms especially hot flushes. This was numerically greater with Premique, though the authors conclude that there was no remarkable difference between them. By year 2, there was a decrease of 64% with Angeliq and 72% with Premique in the number of patients experiencing hot flushes. There was a decrease of 53.8% with Angeliq and 53.5% with Premique in the number of patients experiencing sweating episodes.

In a trial whose primary aim was to assess endometrial effects, there was a statistically significant decrease in hot flushes from baseline at all time points beginning at week 2 ($p=0.008$ in all treatment groups with no significant difference between them).

Other data were also assessed but remain commercially confidential.*

Summary of evidence on comparative safety

The effect of drospirenone 1mg/estradiol 1 mg, drospirenone 2 mg/estradiol 1 mg and drospirenone 3 mg/estradiol 1 mg on the endometrium was the primary outcome of a trial which recruited 1147 post-menopausal amenorrhoeic women who had an intact uterus with negative endometrial biopsy or endometrial thickness <5 mm by vaginal ultrasonography (VUS) at baseline. These formulations were compared with E2 1 mg alone over thirteen 28-day cycles and a biopsy was planned for all subjects at the final visit. Where a biopsy returned insufficient tissue, patients were assessed for endometrial hyperplasia (≥ 5 mm by VUS).

The primary analysis was performed on 791 women after exclusion of those who withdrew before completing one year of treatment with no evidence of endometrial hyperplasia. Endometrial hyperplasia was diagnosed for 8/173 (4.6%) eligible subjects who received estradiol alone and one/149 (0.7%) subject who received 2mg drospirenone/estradiol . No subjects in the other drospirenone groups experienced hyperplasia and no subjects in the study had endometrial cancer.

The proportion of subjects who had a biopsy at any time during treatment and had diagnosis of inactive/atrophic endometrium by biopsy or ultrasonography was 635/966 (66%) overall, 73/197 (37%) for estradiol monotherapy and 149/194 (77%) for the group equivalent to drospirenone 2mg/estradiol 1mg. Proliferative endometrium was the second most common category and was diagnosed in a substantially higher proportion for estradiol monotherapy (51%) than in the drospirenone/estradiol groups (range 6.2% to 16%), and 13% for the group equivalent to Angeliq.

In all studies drospirenone/estradiol was associated with an increase in the proportion of women who experienced bleeding and/or the proportion of time periods during which bleeding occurred and/or a decrease in the incidence of amenorrhoea. In general, bleeding was of low

intensity and the frequency tended to increase during the early cycles after initiation and then to reduce. Both Premique and estradiol monotherapy showed slight advantages over drospirenone/estradiol in terms of bleeding, but in general these differences were either not significant or not tested.

Investigation of the effects of HRT on lipid parameters was the primary aim of a comparison between drospirenone and conjugated oestrogens 0.625 mg/ medroxyprogesterone acetate 5 mg (CEE/MPA, Premique®). Both drospirenone 2 mg/estradiol 1 mg and CEE/MPA showed generally favourable effects on lipids including an increase in HDL-cholesterol which was the primary outcome (+0.21 vs +5.8%). Changes with CEE/MPA were generally larger than with drospirenone/estradiol. However, in general terms, the differences were either not significant or not tested.

Summary of clinical effectiveness issues

Comparative data for this indication come from trials where the investigation of menopausal symptoms were secondary outcomes. There was no comparison with other 'low-dose' preparations e.g. incorporating oestradiol 1 mg or conjugated oestrogens 300 mcg.

Summary of comparative health economic evidence

A cost utility analysis of drospirenone 2mg/estradiol 1mg compared to tibolone is presented. It appears that the basic model structure is as follows:

- All patients start on either drospirenone 2mg/estradiol 1mg or tibolone
- Among those remaining on treatment with drospirenone 2mg/estradiol 1mg or tibolone, quality of life gains, resource use and costs are identical, the only difference being their direct drug costs
- drospirenone 2mg/estradiol 1mg and tibolone are only clinically differentiated by their discontinuation rates
- Those that discontinue their original treatment are subsequently treated with Premique
- Discontinuation of the original treatment leads to a loss in quality of life and some additional switching costs.

Discontinuation rates are estimated from a systematic review of the literature for drospirenone 2mg/estradiol 1mg and tibolone. These rates are annualised on a pro-rata basis; i.e. in studies of three months duration a discontinuation rate of 10% is annualised to a discontinuation rate of 40%. The discontinuation rate for drospirenone 2mg/estradiol 1mg is estimated to be 16%, while the discontinuation rate for tibolone is estimated to be 25%. This results in an average gain from drospirenone 2mg/estradiol 1mg relative to tibolone of 0.011 QALYs, coupled with a saving of £21.67 per patient.

The method for extrapolating discontinuation rates from short terms trials to give a pro-rata annualised rate is open to question. While some sensitivity analyses were carried out the basic premise was not altered.

Drospirenone 2mg/estradiol 1mg is likely to displace products other than tibolone. The market-share weighted-average cost of the 'no-bleed' HRT market is less than the cost of drospirenone 2mg/estradiol 1mg. The exclusion of all 'no-bleed' products other than tibolone from both the systematic review and the economic analysis is questionable.

Patients need a range of products to be available to suit different preferences. drospirenone 2mg/estradiol 1mg is broadly similar in cost to other products, though tibolone and Premique may not be the most appropriate comparators. However, the economic analysis -

- Is restricted to a comparison with tibolone
- Takes no account of possible quality of life differences
- Appears to only differentiate drospirenone 2mg/estradiol 1mg from tibolone by their respective discontinuation rates
- Does not explore other, intuitively reasonable, means of estimating these discontinuation rates.

Given these considerations, the cost effectiveness of drospirenone 2mg/estradiol 1mg relative to tibolone has not been demonstrated, while its cost-effectiveness compared to other treatment options has not been explored.

Patient and public involvement

A Patient Interest Group Submission was not made.

Budget impact

The manufacturer estimates that 2% of the tibolone market will transfer to drospirenone 2mg/estradiol 1mg each year, leading to 10% of the tibolone market switching to drospirenone 2mg/estradiol 1mg by year 5. This translates into 197 patients in year 1, rising to 1,024 in year 5.

This results in a gross cost of £53,000 in year 1, rising to £276,000 by year 5. Given the higher drug cost of tibolone coupled with the greater downstream costs that arise from its higher discontinuation rate, the manufacturer estimates gross savings of £4,300 in year 1 rising to £22,000 by year 5.

However, retaining the manufacturer estimate of patient numbers, own estimates suggest direct drug costs of £1,000 in year 1 and £5,000 in year 5.

Note that the estimate of market penetration amounts to less than 1% of the 'no-bleed' market in year 1, rising to around 3% by year 5.

Guidelines and protocols

Royal College of Obstetricians and Gynaecologists. Hormone Replacement Therapy and Venous Thromboembolism (19). January 2004. www.rcog.org.uk Accessed 25/10/2005

Additional information

SMC has issued the following advice in relation to oral hormone replacement therapy for the treatment of symptoms associated with the menopause.

On 8th November 2004, following a full submission for conjugated oestrogens/ medroxyprogesterone as Premique low-dose, SMC offered the following advice:

The Scottish Medicines Consortium (SMC) has completed its assessment on the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) that conjugated oestrogen medroxyprogesterone is accepted for use within NHS Scotland as hormone replacement therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women with an intact uterus. It is effective in controlling vasomotor symptoms and is associated with lower rates of breast pain and endometrial bleeding compared to other products with higher oestrogen content.

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 15 November 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

** 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. Those shaded grey are additional to those supplied with the submission.

*Schurmann R, Holler T et al. Estradiol and drospirenone for climacteric symptoms in postmenopausal women: a double blind, randomised, placebo-controlled study of the safety and efficacy of three dose regimens. *Climacteric* 2004; 7: 189-196.*

*Warming L, Ravn P et al. Safety and efficacy of drospirenone used in a continuous combination with 17 β -estradiol for prevention of postmenopausal osteoporosis. *Climacteric* 2004; 7:103-111*