PRODUCT INFORMATION

ANGELIQ® 1/2

WARNING

Oestrogens with or without progestogens should not be used for the prevention of cardiovascular disease or dementia.

The Women’s Health Initiative (WHI) study reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 6.8 years of treatment with conjugated oestrogens (0.625 mg) relative to placebo (see CLINICAL TRIALS and PRECAUTIONS).

The WHI study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with conjugated oestrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo (see CLINICAL TRIALS and PRECAUTIONS).

The Women’s Health Initiative Memory Study (WHIMS), a sub-study of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 to 5.2 years of treatment with conjugated oestrogens, with or without medroxyprogesterone acetate, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women (see CLINICAL TRIALS and PRECAUTIONS).

Other doses of conjugated oestrogens and medroxyprogesterone acetate, and other combinations and dosage forms of oestrogens and progestogens were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, oestrogens with or without progestogens should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

NAME OF THE MEDICINE

ANGELIQ 1/2 is a hormone replacement therapy (HRT) preparation containing the oestrogen oestradiol and the progestogen drospirenone. Each red film-coated tablet contains: oestradiol 1.0 mg, drospirenone 2.0 mg.

Oestradiol is oesta-1,3,5(10)-triene-3, 17β-diol, the major estrogenic hormone produced by the human ovary and has the following chemical structure:

![Chemical Structure of Oestradiol](image)

Chemical formula: \( C_{18}H_{24}O_2 \)
Molecular weight: 281.4
Drospirenone is a progestogen. The chemical name for drospirenone is $6\beta, 7\beta, 15\beta, 16\beta$-Dimethylene-3-oxo-17$\alpha$-pregn-4-ene-21, 17-carbolactone and has the following chemical structure:

![Chemical structure of drospirenone]

Chemical formula: $C_{24}H_{30}O_3$
Molecular weight: 366.50
CAS No: 67392-87-4

**DESCRIPTION**

Oestradiol exists mostly as the hemihydrate, which is a non-hygroscopic, stable solid. Oestradiol is a white to almost white, crystalline powder and is practically insoluble in water. The melting point is between 173 and 180°C.

Drospirenone is a white to off-white crystalline powder. It is freely soluble in methylene chloride, soluble in acetone, methanol, sparingly soluble in ethylacetate and ethanol 96% (v/v) and practically insoluble in hexane and water.

ANGELIQ 1/2 tablets contain the following excipients: Lactose, maize starch, pregelatinised maize starch, povidone 25 000, magnesium stearate, hypromellose, macrogol 6000, purified talc, titanium dioxide and iron oxide red.

**PHARMACOLOGY**

**Pharmacodynamic properties**

ANGELIQ 1/2 contains 17$\beta$-oestradiol, which is chemically and biologically identical to endogenous human oestradiol, and the synthetic progestogen, drospirenone. 17$\beta$-oestradiol provides hormone replacement during and after the climacteric. The addition of drospirenone helps to provide bleeding control and opposes the development of endometrial hyperplasia caused by oestrogens.

- Effects of oestradiol

The loss of the ovarian function, accompanied by a depletion of oestrogen and progesterone production, leads to the menopausal syndrome, characterised by vasomotor and organic symptoms. HRT is indicated to eliminate these complaints.

Of all physiological oestrogens, oestradiol is the most potent one with the highest affinity to the oestrogen receptor. Oestrogen target organs include, in particular, uterus, hypothalamus,
pituitary, vagina, breast and bones (osteoclasts).

Other effects of oestrogens include reduction of insulin and blood glucose concentrations, local vasoactive effects mediated by receptors, and receptor-independent effects on vascular smooth muscle. Oestrogen receptors have been identified in the heart and coronary arteries.

HRT has also a positive effect on skin collagen and skin thickness and can retard the process of skin wrinkling.

Oestrogen monotherapy exerts a dose-dependent stimulating effect on mitosis and proliferation of the endometrium and thus increases the frequency of endometrial hyperplasia and hence the risk of endometrial carcinoma. In order to avoid endometrial hyperplasia, a combination with a progestogen is necessary.

- Effects of drospirenone

Drospirenone exerts pharmacodynamic effects very similar to natural progesterone.

**Progestogenic activity**

Drospirenone is a progestogen with a central inhibitory effect on the hypothalamic-pituitary-gonadal axis. In fertile women, drospirenone exerts a contraceptive effect; ovulation is inhibited when drospirenone is administered as a monosubstance. The threshold dose of drospirenone for ovulation inhibition is 2 mg/day. Complete transformation of an estrogen-primed endometrium occurs following a dose of 4 or 6 mg/day for 10 days (= 40 to 60 mg per cycle).

ANGELIQ 1/2 is a continuous combined HRT given with the intent of avoiding the regular withdrawal bleeding associated with cyclic or sequential HRT. During the first months of treatment bleeding and spotting are quite common but decrease with time. With ANGELIQ 1/2 (2 mg drospirenone), the amenorrhea rate rapidly increased to 81% already in cycle 6, 86% in cycle 12, and 91% in cycle 24.

Drospirenone in ANGELIQ 1/2 opposes the development of oestrogen-induced endometrial hyperplasia effectively. After 12 months of treatment with ANGELIQ (drospirenone doses 0.5, 1, 2, or 3 mg) an atrophic/inactive endometrium was achieved in 71 – 77% of the women.

**Antimineralocorticoid Activity**

Drospirenone displays antimineralocorticoid activity (similar to progesterone and spironolactone) affecting the renin-angiotensin-aldosterone system. A dose of 1 mg drospirenone was found to be as potent as about 7 mg spironolactone. Thus, increases in sodium and water excretion are observed due to aldosterone antagonistic effects. Unfavorable oestrogen effects such as increases in blood pressure in susceptible women and sodium and fluid retention resulting in oedema are counterbalanced.

In clinical trials (pooled data from Research Report Nos. AR99, AU18 and A02827 where data was obtained over a period of at least 1 year), the mean systolic and diastolic blood pressure were slightly decreased. After 12 weeks of treatment the mean systolic blood pressure was reduced by -2 mm Hg whereas the diastolic blood pressure was reduced by -2mm Hg (n = 428). With few exceptions, decreases in blood pressure were greater for combinations of oestradiol and drospirenone compared with oestradiol alone. A post hoc performed analysis showed that the effects on blood pressure was more pronounced in patients with borderline hypertension, with a greater decrease observed in mean systolic (-11mm Hg) than diastolic values (–6mm Hg) (n = 71).

In clinical trials with ANGELIQ 1/2 the mean body weight was either unchanged (1 mg
drospirenone) or decreased during the treatment period of 12 months by 1.1-1.2kg (3 or 2 mg drospirenone daily) whereas an increase of 0.5kg was observed in patients treated with oestradiol alone.

**Antiandrogenic Activity**
Like natural progesterone, drospirenone has antiandrogenic properties.

**Effects on Carbohydrate Metabolism**
Drospirenone has no glucocorticoid or antiglucocorticoid activity and has no effect on glucose tolerance and insulin resistance. Glucose tolerance is not compromised by the use of ANGELIQ 1/2.

**Other Properties**
Drospirenone is devoid of estrogenic activity.

**Pharmacokinetics**
- **Drospirenone**

**Absorption**
Orally administered drospirenone is rapidly and almost completely absorbed. Maximum serum concentrations of about 21.9 and 35.9 ng/mL are reached about 1 hour after single and multiple ingestion of ANGELIQ 1/2. Pharmacokinetics of drospirenone are dose-proportional within the dose range of 1 to 4 mg. Bioavailability is between 76 and 85%. The effect of food on absorption of drospirenone was not studied with ANGELIQ 1/2 tablets. However, a food-effect study with another oestrogen/drospirenone combination tablet showed that the extent of absorption (bioavailability) of drospirenone is not affected by concomitant food intake.

**Distribution**
After oral administration, post-maximum serum drospirenone levels decrease in two phases with a mean terminal half-life of about 35 – 39 hours. Drospirenone is bound to serum albumin and does not bind to sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG). Only 3-5% of the total serum drug concentrations are present as free steroid. The mean apparent volume of distribution of drospirenone is 3.7 – 4.2 L/kg.

**Metabolism**
Drospirenone is extensively metabolised after oral administration. The major metabolites in the plasma are the acid form of drospirenone, generated by opening of the lactone ring, and the 4,5-dihydro-drospirenone-3-sulfate, formed by reduction and subsequent sulfation. Based on general knowledge of steroid metabolism, the enzymes 5α-reductase, 3-hydroxysteroid dehydrogenase and 3-hydroxysteroid sulfotransferase are involved in the formation of 4,5-dihydro-drospirenone-3-sulfate. The opening of the lactone ring is presumably catalysed by nonspecific esterases. Drospirenone is also subject to oxidative metabolism catalysed by cytochrome P450 (CYP) 3A4.

**Elimination**
The total clearance of drospirenone from serum is 1.2-1.5 mL/min/kg. Drospirenone is excreted only in trace amounts in unchanged form. The metabolites of drospirenone are excreted with the faeces and urine at a ratio (faeces vs urine) of about 1.2 to 1.4. The half-life of metabolite excretion with the urine and faeces is about 40 hours.

**Steady-State Conditions**
Steady-state conditions are reached after about 10 days of daily treatment with ANGELIQ 1/2. Serum drospirenone levels accumulated by a factor of about 2 to 3 as a consequence of the ratio of terminal half-life and dosing interval.
• Oestradiol

Absorption
Following oral administration, oestradiol is rapidly and completely absorbed. During the absorption and the first liver passage, oestradiol undergoes extensive metabolism, thus reducing the absolute bioavailability of oestrogen after oral administration to about 5% of the dose. Maximum concentrations of about 22 pg/mL were reached 6-8 hours after single oral administration of ANGELIQ 1/2. The effect of food on absorption of oestradiol was not studied with ANGELIQ 1/2 tablets. However, studies with other oestradiol/progestin combination tablets showed that the bioavailability of oestradiol is not affected by concomitant food intake.

Distribution
Following oral administration of ANGELIQ 1/2 only gradually changing serum levels of oestradiol are observed within an administration interval of 24 hours. Because of the large circulating pool of oestrogen sulfates and glucuronides on the one hand and the enterohepatic recirculation on the other hand, the terminal half-life of oestradiol represents a composite parameter that is dependent on all of these processes and is in the range of about 13-20 hours after oral administration.

Oestradiol is bound non-specifically to serum albumin and specifically to SHBG. Only about 1-2% of the circulating oestradiol is present as free steroid, 40-45% is bound to SHBG. The apparent volume of distribution of oestradiol after single intravenous administration is about 1 L/kg.

Metabolism
Oestradiol is rapidly metabolised, and besides oestrone and oestrone sulfate, a large number of other metabolites and conjugates are formed. Oestrone and oestriol are known as pharmacologically active metabolites of oestradiol; only oestrone occurs in relevant concentrations in plasma. At the cellular level oestrogenic potency is highest for oestradiol > oestrone > oestriol. Oestrone reaches about 6-fold higher serum than oestradiol. The serum levels of the oestrone conjugates are about 26 times higher than the corresponding concentrations of free oestrone. The formation of oestrone is catalysed by 17β-hydroxysteroid dehydrogenase and oestrone is further converted to oestrone sulfate by 3-hydroxysteroid sulfotransferase. Several hydroxylation reactions at positions 2, 4 and 16, including the formation of oestriol are catalysed by CYP enzymes of the 3A and 1A families.

Ethnic differences in the metabolism of oestradiol in Caucasian women as compared to Asian or African-American women were reported based on a significantly increased 16α-hydroxylation of oestrone observed in Oriental or African-American women.

Oestradiol is mainly metabolised in the liver but in part also in the gut wall after oral administration and the target organs.

Elimination
The total clearance has been reported to be in the range of 10 to 30 mL/min/kg, indicating that oestradiol is in part also metabolised extrahepatically. Oestradiol and its metabolites are excreted via urine and bile with a half-life of about 1 day.

Steady-State Conditions
Following daily oral administration of ANGELIQ 1/2, oestradiol concentrations reached a steady-state after about five days. Serum oestradiol levels accumulate approx. 2-fold. With a dosing interval of 24 hours, mean steady-state serum levels of oestradiol fluctuate in the range of 20-43 pg/mL following administration of ANGELIQ 1/2.
• Pharmacokinetics in Special Populations

Hepatic Dysfunction

The pharmacokinetics of a single oral dose of 3 mg drospirenone in combination with 1 mg oestradiol was evaluated in 10 female patients with moderate hepatic impairment (Child Pugh B) and 10 healthy female subjects matched for age, weight and smoking history. Mean serum drospirenone concentration-time profiles were comparable in both groups of women during the absorption/distribution phases with similar $C_{\text{max}}$ and $t_{\text{max}}$ values, suggesting that the rate of absorption was not affected by the hepatic impairment. The mean terminal half-life was about 1.8 times greater and an about 50% decrease in apparent oral clearance (CL/f) was seen in volunteers with moderate hepatic impairment as compared to those with normal liver function.

Renal Insufficiency

The effect of renal insufficiency on the pharmacokinetics of drospirenone (3 mg daily for 14 days) were investigated in female subjects with normal renal function (n= 11) and mild (n= 10) and moderate (n= 7) renal impairment. At steady-state of drospirenone treatment, serum drospirenone levels in the group with mild renal impairment (creatinine clearance $\text{CL}_{\text{cr}}$, 50-80 mL/min) were comparable to those in the group with normal renal function ($\text{CL}_{\text{cr}} > 80$ mL/min). The serum drospirenone levels were on average 37% higher in the group with moderate renal impairment ($\text{CL}_{\text{cr}}$, 30-50 mL/min) compared with those in the group with normal renal function. Linear regression analysis of the drospirenone AUC$_{0-24h}$ values in relation to the creatinine clearance revealed a 3.5% increase with a 10 mL/min reduction of creatinine clearance. This slight increase is not expected to be of clinical relevance.

CLINICAL TRIALS

The efficacy and safety of ANGELIQ 1/2 was examined in 4 Phase II/III clinical trials. The women enrolled in these studies were postmenopausal i.e. had their last natural menstrual bleeding at least 6 months prior and serum oestradiol level $\leq 20$ pg/mL and serum follicle stimulating hormone $\geq 50$ U/L. The exclusion criteria for these studies were typical for evaluation of Hormone Replacement Therapies. The pivotal results are presented below.

Research Report No. AR98

The pivotal Phase III study (Research Report No. AR98) was a randomised, double-blind, placebo-controlled study examining the efficacy of ANGELIQ 1/2 and two other oestradiol/drospirenone combinations (1 mg oestradiol with either 1 mg or 3 mg drospirenone) in the prevention of hot flushes and other climacteric symptoms over 16 weeks of treatment. The primary efficacy variable was the frequency and severity of hot flushes, while secondary variables included the frequency and severity of other climacteric complaints, occurrence and severity of vaginal bleeding and safety related parameters. The results for the primary variable are provided in the Table below.

Table 1: Relative change in the number of hot flushes after 16 weeks treatment (Research Report No. AR98)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Mean change$^1$</th>
<th>Standard Deviation</th>
<th>Significant difference (2.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>59</td>
<td>-0.470</td>
<td>0.055</td>
<td>-</td>
</tr>
<tr>
<td>1 mg oestradiol + 1 mg drospirenone</td>
<td>55</td>
<td>-0.856</td>
<td>0.030</td>
<td>Yes$^2$</td>
</tr>
</tbody>
</table>
Research Report No. AR99

A double-blind, placebo-controlled study (Research Report No. AR99) examining the efficacy of ANGELIQ 1/2 and two other oestradiol/drospirenone combinations (1 mg oestradiol with either 1 mg or 3 mg drospirenone) on the prevention of bone mineral density loss over 2 years of treatment was conducted. The primary efficacy variable was hip bone mineral density after 104 weeks of treatment while the secondary variables included hip bone mineral density after 12, 28, 52 and 80 weeks, bone mineral density of lumbar spine, midshaft of the radius and total body. This study was conducted prior to awareness of the ethical implications of the Women’s Health Initiative (WHI) Study and Million Women studies (see below). The results for each treatment group after 6 months (28 weeks) are presented below.

**Table 2:** Percent change in left hip BMD from pre-treatment to end of treatment (104 weeks) in osteopenic patients by treatment (ITT population)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Non-osteopenic patients</th>
<th>Osteopenic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td>Placebo</td>
<td>27</td>
<td>-0.712</td>
</tr>
<tr>
<td>1 mg oestradiol + 1 mg drospirenone</td>
<td>23</td>
<td>2.798&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>ANGELIQ 1/2</td>
<td>30</td>
<td>2.863&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>1 mg oestradiol + 3 mg drospirenone</td>
<td>25</td>
<td>2.846&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup>Significant difference from placebo group (P < 0.05)

**Table 3:** Relative change in hip BMD (28 weeks) (ITT population)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Non-osteopenic patients</th>
<th>Osteopenic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td>Placebo</td>
<td>29</td>
<td>-0.40</td>
</tr>
<tr>
<td>1 mg oestradiol + 1 mg drospirenone</td>
<td>27</td>
<td>0.86</td>
</tr>
<tr>
<td>ANGELIQ 1/2</td>
<td>34</td>
<td>0.76</td>
</tr>
<tr>
<td>1 mg oestradiol + 3 mg drospirenone</td>
<td>30</td>
<td>1.38</td>
</tr>
</tbody>
</table>

**Research Report No. A02827 and A17844**

A double-blind, randomised study (Research Report No. A02827) comparison of ANGELIQ 1/2 and three other oestradiol/drospirenone combinations (1 mg oestradiol with either 0.5 mg, 1 mg or 3 mg drospirenone) with oestradiol (1 mg) to examine effects on the endometrium after 1 year of treatment (13 cycles).

A re-evaluation of the endometrial biopsy samples from Report No. A02827 was conducted (Report No. A17844). The results are presented in the Table below.

**Table 4:** Endometrial biopsy results (Research Report No. A17844)
<table>
<thead>
<tr>
<th></th>
<th>mg</th>
<th>mg + 0.5 mg drospirenone</th>
<th>mg + 1 mg drospirenone</th>
<th>mg + 3 mg drospirenone</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 226</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>197</td>
<td>191</td>
<td>191</td>
<td>194</td>
</tr>
<tr>
<td>No</td>
<td>29</td>
<td>36</td>
<td>40</td>
<td>33</td>
</tr>
<tr>
<td>Cases of hyperplasia</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

1Includes 4 cases of simple hyperplasia with atypia, 3 cases of complex hyperplasia without atypia, and 1 case of complex hyperplasia with atypia
2Includes 1 case of simple type without atypia

Women’s Health Initiative (WHI) Study

Two subsets of the Women’s Health Initiative (WHI), enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either long term oestrogen replacement therapy (ERT) or HRT (conjugated oestrogens alone [0.625 mg per day] and conjugated oestrogens in combination with medroxyprogesterone acetate [0.625 mg/2.5 mg per day]) compared to placebo in the prevention of certain chronic diseases. The study did not evaluate the effects of HRT on menopausal symptoms.

In 8506 postmenopausal women who received oral HRT using a continuous combined regimen of conjugated equine oestrogens (conjugated oestrogens) 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day and 8102 women who received placebo for an average of 5.2 years, adverse effects on the cardiovascular system and the incidence of breast cancer were observed. The Women’s Health Initiative (WHI) study was designed to investigate the efficacy and safety of long-term HRT in preventing coronary heart disease (CHD) in healthy postmenopausal women with an intact uterus. A global index summarising the balance of risks and benefits included an analysis of the primary outcomes CHD and primary adverse outcome, invasive breast cancer, and the following secondary outcomes: stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes. The women enrolled in the study had a mean age at entry of 63.3 years. On average they were overweight (mean body mass index [BMI] = 28.5) and one-third were obese (BMI=≥ 30), 50% were previous or current smokers, one-third had received treatment for high blood pressure and over 10% had raised cholesterol levels requiring medication.

After a mean of 5.2 years of follow-up, the study was stopped because the preset criterion for invasive breast cancer was fulfilled and the global index supported risks exceeding benefits. Estimated hazard ratios (HRs)(nominal 95% confidence intervals [CIs]) were as follows: CHD, 1.29 (1.02-1.63); breast cancer, 1.26 (1.00-1.59); stroke, 1.41 (1.07-1.85); PE, 2.13 (1.39-3.25); colorectal cancer, 0.63 (0.43-0.92); endometrial cancer, 0.83 (0.47-1.47); hip fracture, 0.66 (0.45-0.98), and death due to other causes, 0.92 (0.74-1.14). Corresponding HRs (nominal 95% CIs) for composite outcomes were 1.22 (1.09-1.36) for total cardiovascular disease (arterial and venous disease), 1.03 (0.90-1.17) for total cancer and 1.15 (1.03-1.28) for the global index. The HR for total fractures was 0.76 (0.69-0.85) while total mortality was unchanged [0.98 (0.82-1.18)].

In this study, the absolute excess risks per 10,000 person-years attributable to oestrogen plus progestin were small, i.e. 7 more cases of CHD (37 vs 30), 8 more strokes (29 vs 21), 8 more pulmonary embolies (15 vs 7) and 8 more invasive breast cancers (38 vs 30), while the absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers (10 vs 16), 1 less endometrial cancer (5 vs 6), 5 fewer hip fractures (10 vs 15), 44 total fractures (147 vs 191) and one less death (52 vs 53), than in women not using that form of HRT.
The risks and benefits in women receiving treatment for the short-term management of menopausal symptoms of oestrogen deficiency or for the management of premature menopause were not examined in the WHI study. As well, the study did not include other formulations, dosage regimens or routes of administration of HRT, such as ANGELIQ 1/2 containing oestradiol and drospirenone.

**Oestrogen only arm of WHI study**

In 5310 postmenopausal women who received oral oestrogen replacement therapy using conjugated equine oestrogens (conjugated oestrogens) 0.625 mg/day and 5429 women who received placebo for an average of 6.8 years, adverse effects on the cardiovascular system and the incidence of breast cancer were observed. This Women’s Health Initiative (WHI) study was designed to investigate the efficacy and safety of long-term ERT in preventing coronary heart disease (CHD) in healthy postmenopausal women with hysterectomy. A global index summarising the balance of risks and benefits included an analysis of the primary outcomes CHD and primary adverse outcome, invasive breast cancer, and the following secondary outcomes: stroke, pulmonary embolism (PE), colorectal cancer, hip fracture, and death due to other causes. The women enrolled in the study had a mean age at entry of 63.6 years. On average they were overweight (mean body mass index [BMI] = 30.1) and 45% were obese (BMI > 30), 50% were previous or current smokers, almost 50% had received treatment for high blood pressure and 15% had raised cholesterol levels requiring medication.

After a mean of 6.8 years of follow-up, the study was stopped because CEE did not appear to negatively affect the risk of heart disease or breast cancer but an increased risk of stroke was found. Estimated hazard ratios (HRs)(nominal 95% confidence intervals [CIs]) were as follows: CHD, 0.91 (0.75-1.12); breast cancer, 0.77 (0.59-1.01); stroke, 1.39 (1.10-1.77); PE, 1.34 (0.87-2.06); colorectal cancer, 1.08 (0.75-1.55); hip fracture, 0.61 (0.41-0.91), and death due to other causes, 1.08 (0.88-1.32). Corresponding HRs (nominal 95% CIs) for composite outcomes were 1.12 (1.01-1.24) for total cardiovascular disease (arterial and venous disease), 0.93 (0.81-1.07) for total cancer and 1.01 (0.91-1.12) for the global index. The HR for total fractures was 0.70 (0.63-0.79) while total mortality was unchanged [1.04 (0.88-1.22)].

In this study, the absolute excess risks per 10,000 person-years attributable to oestrogen were small, i.e. 12 more strokes (44 vs 32), 3 more pulmonary emboli (13 vs 10), 1 more colorectal cancer (17 vs 16) and 3 more deaths (81 vs 78), while the absolute risk reductions per 10,000 person-years were 5 fewer cases of CHD (49 vs 54), 7 fewer invasive breast cancers (26 vs 33), 6 fewer hip fractures (11 vs 17), 56 fewer total fractures (139 vs 195), than in women not using that form of HRT.

**Million Women Study**

The results of this study were based on follow up of one million, eighty-four thousand, one hundred and ten (1,084,110) women. The average age of the women at recruitment was 55.9 years and the average period of follow up was 2.6 years for analyses of the cancer incidence and 4.1 years for analyses for mortality. Overall, 50% of the study population had used HRT at some point. There were nine thousand, three hundred and sixty four (9364) newly diagnosed cases of invasive breast cancer and six hundred and thirty seven (637) deaths from breast cancers. The current users of HRT at recruitment were more likely to develop breast cancer and to die from it. Past users of HRT were not at an increased risk of newly diagnosed or fatal disease. The incidence was significantly increased for current users of preparations containing oestrogen only, oestrogen/progestogen and tibolone but the magnitude of the associated risk was greater for the combined treatment than for any other preparation.

**Table 5:** Relative risk of newly diagnosed invasive breast cancer in relation to recency and type, if HRT used

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160322 ANGELIQ 1/2 PI
### HRT use at baseline

<table>
<thead>
<tr>
<th>Cases/population</th>
<th>Relative risk (95% FCI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All never users</td>
<td>2894 / 392757</td>
</tr>
<tr>
<td>All past users</td>
<td>1044 / 150179</td>
</tr>
<tr>
<td>Current users of:</td>
<td></td>
</tr>
<tr>
<td>Oestrogen only</td>
<td>991 / 115383</td>
</tr>
<tr>
<td>Oestrogen-progestogen</td>
<td>1934 / 142870</td>
</tr>
<tr>
<td>Tibolone</td>
<td>184 / 18186</td>
</tr>
<tr>
<td>Other/unknown types</td>
<td>93 / 9548</td>
</tr>
</tbody>
</table>

Relative risk of newly diagnosed invasive breast cancer in relation to recency and type, if HRT used. FCI = floated CI. * Relative to never users, stratified by age, time since menopause, parity and age at first birth, family history of breast cancer, body-mass index, region and deprivation index.

Modified from Lancet 2003; 362:421

An important finding of the Million Women study was that the relative risks of breast cancer were separated from oral, transdermal and implanted oestrogen only formulations.

In terms of absolute risk, after ten years’ use of HRT, it is estimated that there would be 5 (95% CI 3-7) additional breast cancers per 1,000 users of oestrogen only preparations and 19 (95% CI 15-23) additional cancers per 1,000 users of oestrogen/progestogen combinations. The elevated risk reduces after discontinuation of HRT and is effectively lost after 5 years.

### INDICATIONS

Hormone replacement therapy (HRT) for use in the short-term treatment in postmenopausal women with an intact uterus of the climacteric syndrome caused by deficient endogenous oestrogen production due to natural menopause, hypogonadism, castration or primary ovarian failure.

### CONTRAINDICATIONS

HRT should not be started in the presence of any of the conditions listed below. Should any of the conditions appear during HRT use, the product should be stopped immediately.

- Undiagnosed vaginal bleeding
- Known or suspected cancer of the breast
- Known or suspected premalignant conditions or malignancies, if sex steroid-influenced
- Presence or history of liver tumours (benign or malignant)
- Severe hepatic disease
- Presence or history of severe renal disease as long as renal function values have not returned to normal
- Acute arterial thromboembolism (e.g. myocardial infarction, stroke)
- Active deep venous thrombosis, thromboembolic disorders, or a documented history of these conditions
- A high risk of venous or arterial thrombosis
- Severe hypertriglyceridemia
- Pregnancy or lactation
- Known hypersensitivity to the active substances or to any of the excipients.

### PRECAUTIONS

The benefits and risks of HRT must be carefully weighed, including consideration of the
emergence of risks as therapy continues. HRT should be used only in women with menopausal symptoms and ordinarily not for long term use. Oestrogens with or without progestogens should be prescribed at the lowest effective doses and for the shortest duration consistent with the treatment goal and risks for the individual women.

Combination HRT, such as ANGELIQ 1/2 should not be used in hysterectomised women.

ANGELIQ 1/2 cannot be used as a contraceptive.

If any of the conditions/risk factors mentioned below is present or deteriorates, an individual risk-benefit analysis should be done before HRT is started or continued.

The potential for an increased synergistic risk of thrombosis should be considered in women who possess a combination of risk factors or exhibit a greater severity of an individual risk factor. This increased risk may be greater than a simple cumulative risk of the factors. HRT should not be prescribed in case of a negative risk benefit assessment.

**Venous thromboembolism**

Both randomised-controlled and epidemiological studies have suggested an increased relative risk of developing venous thromboembolism (VTE), i.e. deep venous thrombosis or pulmonary embolism. Risk/benefit should therefore be carefully weighed in consultation with the patient when prescribing HRT to women with a risk factor for VTE (see Clinical Trials – WHI study).

Scarabin and others reported the results of a case control study conducted during 1999-2002 in France. The investigators recruited 155 consecutive cases with a first documented episode of VTE of unknown cause (92 with pulmonary embolisms and 63 with deep vein thrombosis), and 381 controls (women admitted to hospital for other reasons) matched for centre, age, and time of recruitment. Overall, 32 (21%) cases and 27 (7%) controls were current users of oral oestrogen replacement therapy (this was defined in this study as oestrogen only therapy or combined HRT), whereas 30 (19%) cases and 93 (24%) controls were current users of transdermal oestrogen replacement therapy. After adjustment for potential confounding variables, the odds ratio for VTE in current users of oral and transdermal oestrogen replacement therapy compared with non-users was 3.5 (95% CI 1.8-6.8) and 0.9 (0.5-1.6), respectively. Estimated risk for VTE in current users of oral oestrogen replacement therapy compared with transdermal oestrogen therapy users was 4.0 (1.9 - 8.3). These results may be interpreted as meaning that (i) the higher risk of VTE as shown in the WHI study has been further supported; and (ii) current but not past use was a risk factor for VTE. Use in the first year was also more risky than later use, a finding that is also consistent with the WHI study.

Generally recognised risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic disposition) and severe obesity. The risk of VTE also increases with age. There is no consensus about the possible role of varicose veins in VTE.

The risk of VTE may be temporarily increased with prolonged immobilisation, major elective or post-traumatic surgery, or major trauma. Depending on the nature of the event and the duration of the immobilisation, consideration should be given to a temporary discontinuation of HRT.

Treatment should be stopped at once if there are symptoms of a thrombotic event or suspicion thereof.

**Arterial thromboembolism**

Two large clinical trials with continuous combined conjugated oestrogens (CEE) and
medroxyprogesterone acetate (MPA) showed a possible increased risk of coronary heart disease (CHD) in the first year of use and no benefit thereafter. One large clinical trial with CEE alone showed a potential reduction of CHD rates in women aged 50-59 and no overall benefit in the total study population. As a secondary outcome, in two large clinical trials with CEE alone or combined with MPA, a 30-40% increased risk of stroke was found. It is uncertain whether these findings also extend to other HRT products or non-oral routes of administration (also see WHI study).

In a study by Hodis et al., of a double-blind, randomised, placebo controlled trial in 226 menopausal women who had at least one coronary artery lesion, oestradiol with or without medroxyprogesterone acetate was administered. The primary efficacy endpoint was the average per participant change between baseline and follow up coronary angiograms in the percent stenosis via quantitative angiography. The study showed that, in women with established coronary artery disease, oestradiol with or without medroxyprogesterone acetate had no significant effect on the progression of atherosclerosis.

Table 6: Results of Quantitative Coronary Angiography in All Lesions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group</th>
<th>Oestrogen group</th>
<th>Oestrogen-progestogen group</th>
<th>P value</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oestrogen group minus control group</td>
</tr>
<tr>
<td>All participants</td>
<td>59</td>
<td>64</td>
<td>53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>36.62 ± 1.15</td>
<td>37.66 ± 1.11</td>
<td>37.10 ± 1.18</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td>1.89 ± 0.78</td>
<td>2.18 ± 0.76</td>
<td>1.24 ± 0.80</td>
<td>0.66</td>
<td>0.29</td>
</tr>
<tr>
<td>95%CI</td>
<td>0.33 to 3.45</td>
<td>0.66 to 3.70</td>
<td>-0.37 to 2.85</td>
<td></td>
<td>-1.88 to 2.46</td>
</tr>
<tr>
<td>Minimal luminal diameter (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-2.87 to 1.57</td>
</tr>
<tr>
<td>At baseline</td>
<td>1.88 ± 0.07</td>
<td>1.81 ± 0.07</td>
<td>1.82 ± 0.07</td>
<td>0.71</td>
<td>-0.02</td>
</tr>
<tr>
<td>Change</td>
<td>-0.13 ± 0.04</td>
<td>-0.15 ± 0.04</td>
<td>-0.11 ± 0.04</td>
<td>0.79</td>
<td>0.02</td>
</tr>
<tr>
<td>95%CI</td>
<td>-0.21 to -0.05</td>
<td>-0.23 to -0.07</td>
<td>-0.19 to -0.03</td>
<td></td>
<td>-0.13 to 0.09</td>
</tr>
</tbody>
</table>

*Modified from Hodis et al NEJM (2003), 349:6 p 540

Gallbladder Disease

Oestrogens are known to increase the lithogenicity of the bile. Some women are predisposed to gallbladder disease during oestrogen therapy.

Dementia

The Women’s Health Initiative Memory Study (WHIMS), included 4532 women 65 years of age and older that were followed up for an average of 4 years. 71% were 65-74 (3726) while 18% (806) were 75 and over and most women (80%) had no prior HRT use. Women treated with 0.625 mg conjugated oestrogens, plus 2.5 mg medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia (DSM-IV criteria). This evidence from clinical studies (WHIMS) with conjugated oestrogen (CEE)-containing preparations suggests that hormonal treatment may increase the risk of probable dementia if initiated in women aged 65 or older. The risk may be decreased if treatment is initiated in early
menopause, as observed in other studies. It is unknown whether these findings also extend to other HRT products.

**Other Conditions**

Treatment should be stopped at once if migrainous or frequent and unusually severe headaches occur for the first time, or if there are other symptoms that are possible premonitory signs of cerebrovascular occlusion.

A general association between HRT use and development of clinical hypertension has not been established. Small increases in blood pressure have been reported in women taking HRT, clinically relevant increases are rare. However, if in individual cases a sustained clinically significant hypertension develops during the use of HRT then withdrawing the HRT may be considered.

Potassium excretion capacity may be limited in patients with renal insufficiency. In a clinical study, drospirenone intake did not show an effect on the serum potassium concentration in patients with mild or moderate renal impairment. A theoretical risk for hyperkalemia can be assumed only for patients whose pretreatment serum potassium is in the upper reference range, and who are additionally using potassium sparing drugs.

Non-severe disturbances of liver function, including hyperbilirubinemas such as Dubin-Johnson syndrome or Rotor syndrome, need close supervision and liver function should be checked periodically. In case of deterioration of markers of liver function, use of HRT should be stopped.

Recurrence of cholestatic jaundice or cholestatic pruritus which occurred first during pregnancy or during previous use of sex steroids necessitates the immediate discontinuation of HRT.

Women with moderately elevated levels of triglycerides need special surveillance. HRT in these women may be associated with a further increase in triglyceride levels bearing the risk of acute pancreatitis.

Although HRT may have an effect on peripheral insulin resistance and glucose tolerance, there is generally no need to alter the therapeutic regimen in diabetics using HRT. However, diabetic women should be carefully monitored while taking HRT.

Certain patients may develop undesirable manifestations of oestrogenic stimulation under HRT such as abnormal uterine bleeding. Frequent or persistent abnormal uterine bleeding during treatment is an indication for endometrial assessment.

Uterine fibroids may increase in size under the influence of oestrogens. If this is observed, treatment should be discontinued.

Should endometriosis be reactivated under treatment, discontinuation of therapy is recommended.

Should there be a suspicion of a prolactinoma, this should be ruled out before starting treatment.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking HRT.

The following conditions have been reported to occur or deteriorate with HRT use. Although the evidence of an association with HRT use is inconclusive, women with these conditions and
treated with HRT should be carefully monitored: epilepsy, benign breast disease, asthma, migraine, porphyria, otosclerosis, systemic lupus erythematosus and chorea minor.

In women with hereditary angioedema, exogenous oestrogens may induce or exacerbate symptoms of angioedema.

**Genotoxicity**

There is limited evidence available in the literature suggesting that oestradiol may be weakly genotoxic at high doses. No evidence could be found for an increase in the rate of gene mutation in bacterial or mammalian cells, but there was some evidence for the induction of chromosomal aberrations and aneuploidy in mammalian cells, and two groups reported an increase incidence of sister chromatid exchanges, indicative of DNA damage. Neither of these latter effects were induced by oestradiol in human lymphocyte cultures. Importantly, there was no evidence of micronuclei formation in well controlled rodent bone marrow assays.

Although interactions between drospirenone and DNA of liver cells which indicate a genotoxic potential were found in vitro and in vivo studies in rats, no such finding was observed in human liver cells in vitro. Furthermore, mutagenicity tests gave no indication of a mutagenic potential of the compound. Genotoxic potential of the oestradiol-drospirenone combination has not been investigated.

**Carcinogenicity**

Carcinogenicity studies have not been performed with the combination of drospirenone and oestradiol. However, studies have been performed for oestradiol and drospirenone, the active components of ANGELIQ 1/2. Supra-physiological doses of oestradiol have been associated with the induction of tumours in oestrogen-dependent target organs in all rodent species tested. The relevance of these findings with respect to humans has not been established. However, it must be borne in mind that sex steroids can promote the growth of certain hormone dependent tissues and tumours.

In long-term oral carcinogenicity studies in mice and rats, drospirenone alone did not increase the incidence of neoplastic lesions. Exposure to drospirenone (based on AUC) was up to ~5-fold (mice) and 12-fold (rats) that anticipated in humans at the recommended clinical dose.

**Breast Cancer**

A meta-analysis from 51 epidemiological studies has reported an increased risk of having breast cancer diagnosed in women who have used HRT for several years. The findings may be due to an earlier diagnosis, the biological effects of HRT, or a combination of both. The relative risk increases with duration of treatment (by 2.3% per year of use). This is comparable to the increased risk of breast cancer observed in women with every year of delay of natural menopause (2.8% per year of delay). The increased risk gradually disappears during the course of the first five years after the cessation of HRT. Breast cancers found in women using HRT are more likely to be localised to the breast than those found in non-users.

The increased risk of having breast cancer diagnosed in women who have used HRT for several years was confirmed in the WHI study (see CLINICAL TRIALS).

In the Million Women study this increased risk emerged towards the end of the first year of treatment (see CLINICAL TRIALS).

HRT increases the density of mammographic images which may adversely affect radiological detection of breast cancer in some cases.
Ovarian Cancer

Ovarian cancer is less prevalent than breast cancer. A meta-analysis from 52 epidemiological studies reported that the overall risk of being diagnosed with ovarian cancer is slightly increased for users of oestrogen-only and combined HRT compared to women who have never used HRT (prospective studies: RR 1.20, 95% CI 1.15-1.26; all studies combined: RR 1.14, 95% CI 1.10-1.19). In women currently using HRT the risk of ovarian cancer was further increased (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

These associations were not shown in the WHI.

Furthermore, an effect of duration of exposure has not been consistently shown, but the risk may be more relevant with long-term use (several years).

Endometrial Cancer

Prolonged exposure to unopposed oestrogens increases the risk of development of endometrial hyperplasia or carcinoma. Studies have suggested that the appropriate addition of progestogens to the regimen eliminates this increase in risk. The addition of drospirenone opposes the development of endometrial hyperplasia caused by oestrogens.

Liver Tumours

In rare cases benign, and even more rarely, malignant liver tumours have been observed after the use of hormonal substances such as those contained in HRT products. In isolated cases, these tumours led to life-threatening intra-abdominal haemorrhage. A hepatic tumour should be considered in the differential diagnosis if upper abdominal pain, enlarged liver, or signs of intra-abdominal haemorrhage occur.

Use in Pregnancy

Pregnancy – Category B3

Drospirenone and/or its metabolites crossed the placenta and entered the fetus when administered orally to pregnant rats and rabbits. No data are available for the combination of oestradiol and drospirenone but treatment of pregnant rats with a combination of drospirenone and ethinyloestradiol resulted in a dose-dependent increased incidence of embryolethality due to increased pre- and post-implantation losses. There was no indication of teratogenic effects of drospirenone in rats or rabbits.

Dose-dependent feminisation of male fetuses and virilisation of female fetuses were seen following administration of a combination of drospirenone and ethinyloestradiol to female rats in the last third of pregnancy. Feminising effects in male fetuses were consistent with drospirenone’s anti-androgenic activity and were observed at an estimated systemic exposure approximately 12-20 fold that anticipated clinically (based on AUC). Virilisation of female fetuses was seen following systemic drospirenone exposure of approximately 3-8 fold that anticipated clinically (based on AUC). This effect has previously been described for oestrogens in rats. When pregnant monkeys received a combination of drospirenone and ethinyloestradiol by daily oral administration during the major period of organogenesis and sexual organ differentiation, abortion rates were increased in a dose-dependent manner. However, there were no indications of teratogenicity.

The potential risk for humans is unknown. Epidemiological studies to date have not revealed a teratogenic effect when women were inadvertently exposed to oestrogen/progestogen.
combinations during early pregnancy.

ANGELIQ 1/2 should not be used during pregnancy (see CONTRAINDICATIONS). Pregnancy should be ruled out before the start of therapy. If pregnancy occurs during medication with ANGELIQ 1/2, treatment should be discontinued promptly.

Use in Lactation

ANGELIQ 1/2 should not be used during lactation (see CONTRAINDICATIONS). Small amounts of drospirenone and oestrogen are excreted with the milk. Oestrogen administration to breastfeeding mothers has been shown to decrease the quantity and quality of milk.

Paediatric Use

ANGELIQ 1/2 is not indicated for use in children or adolescents.

Patients with Hepatic Impairment

In women with mild or moderate hepatic impairment, drospirenone is well tolerated (see Pharmacokinetics). ANGELIQ 1/2 is contraindicated in women with severe hepatic disease (see CONTRAINDICATIONS).

Patients with Renal Impairment

In women with mild or moderate renal impairment, a slight increase of drospirenone exposure was observed but is not expected to be of clinical relevance (see Pharmacokinetics). ANGELIQ 1/2 is contraindicated in women with severe renal disease (see CONTRAINDICATIONS).

Medical Examination/Consultation

A complete medical history should be taken and a physical examination should be conducted prior to the initiation or reinstitution of HRT, guided by Contraindications and Precautions and should be repeated periodically. The frequency and nature of these examinations should be based on established practice guidelines and be adapted to the individual woman, but should generally include pelvic organs, including routine cervical cytology, abdomen, breasts and blood pressure.

Effect on Laboratory Tests

The use of sex steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins e.g. sex hormone binding globulin and lipid/lipoprotein fractions and parameters of coagulation and fibrinolysis. Changes generally remain within the reference range. Glucose tolerance was not compromised by the use of ANGELIQ 1/2.

Effects on Ability to Drive and Use Machines

No effects on the ability to drive and use machines have been observed.

INTERACTION WITH OTHER MEDICINES

The Product Information of concomitant medicines should be consulted to identify potential interactions.
Effects of Other Medicines on ANGELIQ 1/2

Interactions can occur with medicines that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to changes in the uterine bleeding profile and/or reduction of the therapeutic effect.

Substances increasing the clearance of sex hormones (diminished efficacy by enzyme-induction), e.g.:

Phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John’s wort.

Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy, enzyme induction may be sustained for about four weeks.

Substances with variable effects on the clearance of sex hormones, e.g.:

When co-administered with sex hormones, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of oestrogen or progestin or both. These changes may be clinically relevant in some cases.

Substances decreasing the clearance of sex hormones (enzyme inhibitors)

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. ketoconazole, itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the progestin or the oestrogen or both.

The clinical relevance of potential interactions with enzyme inhibitors remains unknown.

Interaction with Alcohol

Acute alcohol ingestion during use of HRT may lead to elevations of circulating oestradiol levels.

Effect of ANGELIQ 1/2 on Other Medicines

In vitro, drospirenone has demonstrated a capacity to inhibit CYP1A1, CYP2C9 and CYP2C19 and CYP3A4.

Based on in vitro inhibition studies drospirenone showed 50% inhibition of CYP1A1, 2C9, 2C19 and 3A4 at concentrations which were about two to three orders of magnitude higher than the maximum free drospirenone serum concentrations at steady-state after administration of ANGELIQ 1/2.

In a clinical drug-drug interaction study in 24 postmenopausal women [12 women with homozygous (wild type) CYP2C19 genotype, extensive metabolisers (EM) and 12 women with heterozygous CYP2C19 genotype, intermediate metabolisers (IM)] who received oral doses of 3 mg drospirenone for 14 days and omeprazole, 40 mg once before and once on the last day of the 14-days of drospirenone treatment, no significant influence from drospirenone co-administration on the AUC of the CYP2C19 substrate OMP and the CYP2C19 enzyme product 5-OHOMP was observed. There was no significant influence from drospirenone co-administration on AUC of the CYP3A4 enzyme product OMPSO in either IM or EM groups. Thus the results of this study did not demonstrate an inhibition of the enzymes CYP2C19 and CYP3A4 by drospirenone at clinically relevant steady-state exposure at 3 mg/day dosing regimen.
Based on *in vivo* interaction studies in female volunteers using simvastatin or midazolam as marker substrates, a clinically relevant interaction of drospirenone at doses of 3 mg with the CYP enzyme mediated metabolism of other medicines is unlikely.

Antagonism of the effectiveness of anticoagulants may occur.

*Pharmacodynamic Interaction with Antihypertensive Medicines*

Women treated with ANGELIQ 1/2 and antihypertensive medications may experience an additional decrease in blood pressure. Concomitant use of ANGELIQ 1/2, non-steroidal anti-inflammatory medicines and antihypertensive medications may cause a small increase in serum potassium, more pronounced in diabetic women.

**ADVERSE EFFECTS**

Serious undesirable effects associated with the use of HRT are also mentioned under PRECAUTIONS.

Serious adverse reactions are arterial and venous thromboembolic events, and breast cancer. For venous and arterial thromboembolic events, breast cancer and migraine, see CONTRAINDICATIONS and PRECAUTIONS.

The table below (HARTS Body System and Dictionary Term) attributes frequencies to the undesirable effects of ANGELIQ 1/2. These frequencies are based on the frequencies of adverse events, which were recorded in 4 phase III clinical studies (n = 1532 women at risk) and considered at least possibly related to ANGELIQ 1/2 treatment (containing 1, 2 or 3 mg drospirenone).

During the first few months of treatment, bleeding and spotting can occur. These are usually temporary and normally disappear after continued treatment (see Pharmacodynamics-Effects of drospirenone). The frequency of bleeding decreases with the duration of treatment. Breast pain was a very common symptom, reported in approximately one out of five women.

<table>
<thead>
<tr>
<th>Common (≥ 1/100, &lt; 1/10)</th>
<th>Uncommon (≥ 1/1000, &lt; 1/100)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a whole</strong></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain or bloating, Asthenia, Pain in extremity.</td>
<td>Pain in back or pelvis, Chills, Malaise, Laboratory test abnormal</td>
</tr>
<tr>
<td><strong>Cardiovascular system</strong></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>Migraine, Hypertension, Chest pain, Palpitation, Varicose veins, Venous thrombosis, Superficial thrombophlebitis, Vasodilatation.</td>
</tr>
<tr>
<td><strong>Digestive</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>Gastrointestinal disorder, Increased appetite, Liver function test abnormal</td>
</tr>
<tr>
<td><strong>Metabolic and nutritional</strong></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>Generalised or localised oedema, Weight gain, Hyperlipidaemia.</td>
</tr>
<tr>
<td><strong>Musculoskeletal system</strong></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>Muscle cramps, Arthralgia.</td>
</tr>
<tr>
<td><strong>Nervous system</strong></td>
<td></td>
</tr>
<tr>
<td>Headache, Mood swings, Hot flushes, Nervousness.</td>
<td>Insomnia, Dizziness, Libido decreased, Concentration ability impaired, Paraesthesia,</td>
</tr>
<tr>
<td>Common (≥ 1/100, &lt; 1/10)</td>
<td>Uncommon (≥ 1/1000, &lt; 1/100)</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td><strong>Respiratory system</strong></td>
<td>Sweating increased, Anxiety, Dry mouth, Vertigo.</td>
</tr>
<tr>
<td><strong>Skin and appendages</strong></td>
<td>Dyspnoea</td>
</tr>
<tr>
<td>Benign breast neoplasms, Breast enlargement.</td>
<td>Alopecia, Skin or hair disorder, Hirsutism, Breast carcinoma, Breast engorgement.</td>
</tr>
<tr>
<td><strong>Special senses</strong></td>
<td>Taste disturbance</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Urogenital</strong></td>
<td></td>
</tr>
<tr>
<td>Uterine fibroids enlarged, Cervix neoplasm, Leucorrhoea.</td>
<td>Vulvovaginitis, Endometrial or cervical disorder, Bleeding, Dysmenorrhoea, Ovarian cyst, Urinary tract infections or incontinence.</td>
</tr>
</tbody>
</table>

In exceptional cases erythema nodosum, erythema multiforme, chloasma and haemorrhagic dermatitis have been reported in women receiving HRT.

In a post-hoc analysis of the prospective cohort of the Nurses’ Health Study, occurrences of inflammatory bowel disease have been reported in HRT users. Based on current scientific knowledge, there is no clear evidence for a causal relationship between HRT use and inflammatory bowel disease.

Adverse reactions with delayed onset of symptoms which are considered to be related to the group of continuous combined products for HRT are listed below (see PRECAUTIONS).

**Tumours**

- Liver tumours (benign and malignant)
- Sex steroid influenced malignancies and pre-malignant conditions (if such a condition is known, this constitutes a contraindication for the use of ANGELIQ 1/2)
- Oestrogen-only and combined oestrogen-progestogen HRT has been associated with a slightly increased risk of ovarian cancer in epidemiological studies. The risk may be more relevant with long-term use (several years) (see PRECAUTIONS)

**Other Conditions**

- Gall bladder disease (see PRECAUTIONS)
- Dementia (see PRECAUTIONS)
- Endometrial cancer (see PRECAUTIONS)
- Hypertension (see PRECAUTIONS)
- Disturbances of liver function
- Hypertriglyceridaemia (see PRECAUTIONS)
- Changes in glucose tolerance or effect on peripheral insulin resistance
- Increase in size of uterine fibroids
- Reactivation of endometriosis
- Prolactinoma (risk of aggravation of hyperprolactinaemia or induction of tumour growth)
- Chloasma
- Jaundice and/or pruritus related to cholestasis
- Occurrence or deterioration of conditions for which association with HRT use is not conclusive: epilepsy, benign breast disease, asthma, porphyria, systemic lupus erythematosus, otosclerosis, chorea minor
- In women with hereditary angioedema, exogenous oestrogens may induce or exacerbate
symptoms of angioedema
• Hypersensitivity (incl. symptoms such as rash and urticaria)

DOSAGE AND ADMINISTRATION

HRT should only be continued as long as the benefit in alleviation of severe symptoms outweighs the risk.

How to Start ANGELIQ 1/2

Women who do not take oestrogens or women who change from a continuous combination product may start treatment at any time. Patients changing from a sequential combined HRT treatment should be started at the end of the scheduled bleeding.

Dosage

One tablet is taken daily. Each blister pack is for 28 days of treatment.

Administration

The tablets are to be swallowed whole with some liquid irrespective of food intake. Treatment is continuous, which means that the next pack follows immediately without a break. The tablets should preferably be taken at the same time every day. In case a tablet is forgotten, it should be taken as soon as possible. If more than 24 hours have elapsed no extra tablet needs to be taken. If several tablets are forgotten, bleeding may occur.

OVERDOSAGE

In clinical studies, up to 100 mg of drospirenone and oestrogen/progestogen preparations containing 4 mg oestradiol were well tolerated. Overdose may cause nausea and vomiting and withdrawal bleeding may occur in some women. There are no specific antidotes and therefore treatment should be symptomatic.

PRESENTATION AND STORAGE CONDITIONS

Shelf Life

The expiry date is marked on the pack.

Nature and Contents of Container

Transparent polyvinyl film (250 μm)/aluminium foil (20 μm) blister strips of 28 tablets. Calendar-pack containing 1 x 7, 1 x 28, 2 x 28, 3 x 28 & 4 x 28 tablets.

Not all pack sizes may be marketed.

Film-Coated Tablets - small, round, red tablet, one side embossed with the letters DL in a regular hexagon.

Instructions for Use/Handling

Store all medicines properly, according to the storage conditions printed on the pack and keep them out of reach of children. Store below 30°C.
NAME AND ADDRESS OF THE SPONSOR

Bayer Australia Ltd
875 Pacific Highway
Pymble
NSW 2073
AUSTRALIA

POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION IN THE ARTG

30 November 2004

DATE OF MOST RECENT AMENDMENT

22 March 2016

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