ESTRADIOL/DROSPIRENONE

CORE SAFETY PROFILE

4.3 Contraindications

- Undiagnosed genital bleeding
- Known, past or suspected cancer of the breast
- Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer)
- Untreated endometrial hyperplasia
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal
- Known thrombophilic disorders (e.g. protein C protein S, or antithrombin deficiency, see section 4.4
- Severe renal insufficiency or acute renal failure
- Known hypersensitivity to the active substances or to any of the excipients
- Porphyria

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.

Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

Medical examination/follow-up

Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse. Investigations, including appropriate imaging tools, e.g. mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need supervision

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Angeliq, in particular:

- Leiomyoma (uterine fibroids) or endometriosis,
- Risk factors for thromboembolic disorders (see below)
- Risk factors for oestrogen dependent tumours, e.g. 1st degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache

- Systemic lupus erythematosus
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contra-indication is discovered and in the following situations:
- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache
- Pregnancy

Endometrial hyperplasia and carcinoma

In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among oestrogen-only users varies from 2- to 12-fold greater compared with non-users, depending on the duration of treatment and oestrogen dose (see section 4.8). After stopping treatment risk may remain elevated for at least 10 years.

The addition of a progestogen cyclically for at least 12 days per month / 28-day cycle or continuous combined oestrogen-progestagen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.

Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

Breast cancer

The overall evidence suggests an increased risk of breast cancer in women taking combined oestrogen-progestagen and possibly also oestrogen-only HRT, that is dependent on the duration of taking HRT.

The randomised placebo-controlled trial, the Women's Health Initiative study (WHI), and epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestagen for HRT that becomes apparent after about 3 years (see section 4.8). The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment.

HRT, especially oestrogen-progestogen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Venous thromboembolism

HRT is associated with a 1.3- to 3-fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see section 4.8).

Generally recognised risk factors for VTE include use of oestrogens, older age, major surgery, a personal history or family history obesity (BMI > 30 kg/m^2) pregnancy/postpartum period, systemic lupus erythematosus (SLE) and cancer. There is no consensus about the possible role of varicose veins in VTE.

Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. . HRT is therefore contraindicated in these patients (see section 4.3).

As in all postoperative patients, prophylactic measures need to be considered to prevent VTE following surgery. If prolonged immobilization is to follow elective surgery temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilized.

In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening). If a thrombophilic defect is identified which segregates with thrombosis in family members or of the defect is 'severe' (e.g. antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated.

Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease (CAD)

There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen and progestagen or oestrogen-only HRT. The relative risk of CAD during use of combined oestrogen and progestagen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to oestrogen and progestagen use is very low in healthy women close to menopause, but will rise with more advanced age.

Ischaemic stroke

Combined oestrogen-progestagen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see section 4.8).

Ovarian cancer

Ovarian cancer is much rarer than breast cancer. Long-term (at least 5-10 years) use of oestrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer (see section 4.8). Some studies including the WHI trial suggest that the long-term use of combined HRT may confer a similar, or slightly smaller risk (see section 4.8).

Other conditions

Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.

Women with pre-existing hypertriglyceridemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition.

Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, ceruloplasmin).

HRT use does not improve cognitive function. There is some evidence of increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65.

The progestin component in Angeliq is an aldosterone antagonist exhibiting weak potassium sparing properties. In most cases, no increase of serum potassium levels is to be expected. In a clinical study, however, in some patients with mild or moderate renal impairment and concomitant use of potassium-sparing medicinal products (such as ACE inhibitors, angiotensin II receptor antagonists or NSAIDs) serum potassium levels slightly, but not significantly increased during drospirenone intake. Therefore, it is recommended to check serum potassium during the first month of treatment in patients presenting with renal insufficiency and pretreatment serum potassium in the upper reference range, and particularly during concomitant use of potassium sparing medicinal products (see also section 4.5).

Women with elevated blood pressure may experience a decrease in blood pressure under treatment with Angeliq due to the aldosterone antagonist activity of drospirenone (see section 5.1). Angeliq should not be used to treat hypertension. Women with hypertension should be treated according to hypertension guidelines.

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.

Each tablet of this medicinal product contains 46 mg lactose per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose-free diet should take this amount into consideration.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on Angeliq

The metabolism of oestrogens [and progestogens] may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamezapine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St. John’s wort (Hypericum perforatum) may induce the metabolism of oestrogens (and progestogens).

Clinically, an increased metabolism of oestrogens and progestogens may lead to decreased effect and changes in the uterine bleeding profile.

The main metabolites of drospirenone are generated without involvement of the cytochrome P450 system. Inhibitors of this enzyme system are therefore unlikely to influence the metabolism of drospirenone.

Interaction of Angeliq with other medicinal products

Based on in vitro inhibition studies and on in vivo interaction studies in female volunteers receiving steady-state doses of 3 mg drospirenone per day and omeprazole, simvastatin, or midazolam as marker substrate, a clinically relevant interaction of drospirenone with the cytochrome P450 enzyme mediated metabolism of other drugs is unlikely.

Concomitant use of Angeliq and either NSAIDs or ACE inhibitors / angiotensin II receptor antagonists is unlikely to increase serum potassium. However, concomitant use of all these three types of medications together may cause a small increase in serum potassium, which is more pronounced in diabetic women. Hypertensive women treated with Angeliq and antihypertensive medications may experience an additional decrease in blood pressure (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy

Angeliq is not indicated during pregnancy. If pregnancy occurs during medication with Angeliq, treatment should be discontinued promptly. No clinical data on exposed pregnancies are available for drospirenone. Animal studies have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of oestrogens with other progestogens have not indicated a teratogenic or foetotoxic effect.

Lactation

Angeliq is not indicated during lactation.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The table below reports adverse reactions by MedDRA system organ classes (MedDRA SOCs). The frequencies are based on clinical trial data. The adverse reactions were recorded in 7 Phase III clinical studies (n=2424 women) and considered as at least possibly causally related to Angeliq (E2 1 mg / DRSP doses 0.5, 1, 2, or 3 mg).
The most commonly reported adverse reactions were breast pain (> 10%) and during the first few months of treatment, bleeding and spotting (> 10%). Bleeding irregularities usually subside during continued treatment (see section 5.1). The frequency of bleeding decreases with the duration of treatment.

System Organ Class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)	Rare (< 1/1000)
Blood and lymphatic system disorders			Anaemia
Metabolism and nutrition disorders		Weight increase or weight decrease, anorexia, increased appetite, hyperlipemia	
Psychiatric disorders	Depression, emotional lability, nervousness	Sleep disorder, anxiety, libido decreased	
Nervous system disorders	Headache	Paresthesia, concentration ability impaired, dizziness	Vertigo
Eye disorders		Eye disorder, visual disturbance	
Ear and labyrinth disorders			Tinnitus
Cardiac disorders		Palpitation	
Vascular disorders		Embolism, venous thrombosis, hypertension, migraine, thrombophlebitis, varicose veins	
Respiratory, thoracic and mediastinal disorders		Dyspnoea	
Gastrointestinal disorders	Abdominal pain, nausea, abdomen enlarged	Gastrointestinal disorder, diarrhea, constipation, vomiting, dry mouth, flatulence, taste disturbance	
Hepatobiliary disorders		Liver function test abnormal	Cholelithiasis
Skin and subcutaneous tissue disorders		Skin disorder, acne, alopecia, pruritus, rash, hirsutism, hair disorder	
Musculoskeletal and connective tissue disorders		Pain in extremity, back pain, arthralgia, muscle cramps	Myalgia
Renal and urinary disorders		Urinary tract disorder, urinary tract infection	
Reproductive system and breast disorders	Benign breast neoplasm, breast enlargement, uterine fibroids enlarged, benign neoplasm of cervix uteri, menstrual disorder, vaginal discharge	Breast carcinoma, endometrial hyperplasia, benign uterine neoplasm, fibrocystic breast, uterine disorder, ovarian disorder, cervix disorder, pelvic pain, vulvovaginal disorder, vaginal candidiasis, vaginitis, vaginal dryness	Salpingitis, galactorrhoea
General disorders and administration site conditions	Asthenia, localized oedema	Generalized oedema, chest pain, malaise, sweating increased	Chills

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Additional information on special populations

The following, undesirable effects classified as at least possibly related to Angeliq treatment by the investigator, were recorded in 2 clinical studies in hypertensive women.

Metabolism and nutrition disorders
Hyperkalemia

Cardiac disorders
Cardiac failure, atrial flutter, QT interval prolonged, cardiomegaly.

Investigations
Blood aldosterone increased.

The following undesirable effects have been reported in association with HRT products: Erythema nodosum, eythema multiforme, chloasma and hemorrhagic dermatitis.

Breast cancer risk

An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestagen therapy for more than 5 years. Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestagen combinations. The level of risk is dependent on the duration of use (see section 4.4). Results of the largest randomised placebo-controlled trial (WHI study) and largest epidemiological study (MWS) are presented.

Million Women Study – estimated additional risk of breast cancer after 5 years of use

Age range (years)	Additional cases per 1000 never-users of HRT over a 5-year period [a]	Risk ratio [b]	Additional cases per 1000 HRT users over 5 years (95% CI)
		Oestrogen-only HRT	
50 - 65	9 - 12	1.2	1 - 2 (0 - 3)
		Combined oestrogen-progestagen	
50 - 65	9 - 12	1.7	6 (5 - 7)

a Taken from baseline incidences in developed countries.

b Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use.

Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

US WHI studies - additional risk of breast cancer after 5 years of use			
Age range (years)	**Incidence per 1000 women in placebo arm over 5 years**	**Risk ratio & 95% CI**	**Additional cases per 1000 HRT users over 5 years (95% CI)**
		CEE oestrogen-only	
50 - 79	21	0.8 (0.7 - 1.0)	-4 (-6 - 0) [a]
		CEE + MPA oestrogen & progestagen [b]	
50 - 79	17	1.2 (1.0 - 1.5)	+4 (0 - 9)

a WHI study in women with no uterus, which did not show an increased in risk of breast cancer.

b When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.

Endometrial cancer risk

Postmenopausal women with a uterus

The endometrial cancer risk is about 5 in every 1000 women with an uterus not using HRT. In women with a uterus, use of oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4). Depending on the duration of oestrogen-only use and oestrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1000 women between the ages of 50 and 65.

Adding a progestagen to oestrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study the use of five years of combined (sequential or continuous) HRT did not increase risk of endometrial cancer (RR of 1.0 (0.8-1.2)).

Ovarian cancer

Long-term use of oestrogen-only and combined oestrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer. In the Million Women Study 5 years of HRT resulted in 1 extra case per 2500 users.

Risk of venous thromboembolism

HRT is associated with a 1.3 - 3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HT (see section 4.4). Results of the WHI studies are presented:

WHI Studies - additional risk of VTE over 5 years of use			
Age range (years)	**Incidence per 1000 women in placebo arm over 5 years**	**Risk ratio & 95% CI**	**Additional cases per 1000 HRT users**
		Oral oestrogen-only [a]	
50 - 59	7	1.2 (0.6 - 2.4)	1 (-3 - 10)
		Oral combined oestrogen-progestagen	
50 - 59	4	2.3 (1.2 - 4.3)	5 (1 - 13)

[a] Study in women with no uterus.

Risk of coronary artery disease

The risk of coronary artery disease is slightly increased in users of combined oestrogen-progestagen HRT over the age of 60 (see section 4.4).

Risk of ischaemic stroke

The use of oestrogen-only and oestrogen-progestagen therapy is associated with an up to 1.5-fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.

This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age, see section 4.4.

WHI studies combined - additional risk of ischaemic stroke over 5 years of use			
Age range (years)	**Incidence per 1000 women in placebo arm over 5 years**	**Risk ratio & 95% CI**	**Additional cases per 1000 HRT users over 5 year**
50 - 59	8	1.3 (1.1 – 1.6)	3 (1 – 5)

[a] No differentiation was made between ischaemic and haemorrhagic stroke.

Other adverse reactions have been reported in association with oestrogen/progestogen treatment

- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.
- Probable dementia over the age of 65 (see section 4.4).

4.9 Overdose

In clinical studies in male volunteers doses up to 100 mg of drospirenone were well tolerated. Based on general experience with combined oral contraceptives, symptoms that may possibly occur are nausea and vomiting and – in young girls and some women – vaginal bleeding. There are no specific antidotes, and, therefore, treatment should be symptomatic.