SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Angeliq film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 1 mg oestradiol (as oestradiol hemihydrate) and 2 mg drospirenone.

Excipient with known effect: 46 mg lactose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Medium red, round tablet with convex faces, one side embossed with the letters DL in a regular hexagon.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.
(See also section 4.4)

The experience treating women older than 65 years is limited.

4.2 Posology and method of administration

Women who do not take hormone replacement therapy (HRT) or women who change from another continuous combined product may start treatment at any time. Women changing from a cyclic, sequential combined HRT regimen, treatment should begin the day following completion of the prior regimen.

Posology

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

Method of 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. If 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, vaginal bleeding may occur.

For treatment of post menopausal symptoms, the lowest effective dose should be used.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also section 4.4) should be used.

Additional information on special populations

Paediatric population

Angeliq is not indicated for use in children and adolescents.

Geriatric patients

There are no data suggesting a need for dosage adjustment in elderly patients. In women aged 65 years or older, see section 4.4.

Patients with hepatic impairment

In women with mild or moderate hepatic impairment, drospirenone is well tolerated (see section 5.2. Pharmacokinetic properties). Angeliq is contraindicated in women with severe hepatic disease (see section 4.3).

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 section 5.2). Angeliq is contraindicated in women with severe renal disease (see section 4.3).

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
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- 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-progestogen 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-progestogen 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-progestogen 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.

Ovarian cancer

Ovarian cancer is much rarer than breast cancer.

Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only or combined oestrogen-progestagen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.

Some other studies, including the WHI trial, suggest that use of combined HRTs may be associated with a similar or slightly smaller risk (see section 4.8).

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 immobilisation 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 mobilised.

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 if 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-progestogen or oestrogen-only HRT.

The relative risk of CAD during use of combined oestrogen-progestogen 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-progestogen use is very low in healthy women close to menopause, but will rise with more advanced age.

Ischaemic stroke

Combined oestrogen-progestogen 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).

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

Note: The prescribing information of concomitant medications should be consulted to identify potential interactions:

Effects of other medicinal products on Angeliq

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

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. barbiturates, phenytoin, primidone, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz) and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and products containing the herbal remedy St. John's Wort (hypericum perforatum).

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

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 4 weeks.

Substances with variable effects on the clearance of sex hormones:

When co-administered with sex hormones, many combinations of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV inhibitors can increase or decrease plasma concentrations of oestrogen or progestins. The net effect of these changes may be clinically relevant in some cases.

Therefore, the prescribing information of concomitant HIV/HCV medications should be consulted to identify potential interactions and any related recommendations.

Substances decreasing the clearance of sex hormones (enzyme inhibitors)

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the progestin or the oestrogen or both. In a multiple dose study with a drospirenone (3 mg/day) / oestradiol (1.5 mg/day) combination, co-administration of the strong CYP3A4 inhibitor ketoconazole for 10 days increased the AUC(0 24h) of drospirenone 2.30 fold (90%CI: 2.08, 2.54). No change was observed for oestradiol, although the AUC(0 24h) of its less potent metabolite oestrone increased 1.39-fold (90%CI: 1.27, 1.52).

Effect of Angeliq on other medicinal products

In vitro, drospirenone is capable to inhibit weakly to moderately the cytochrome P450 enzymes CYP1A1, CYP2C9, CYP2C19 and CYP3A4.

Based on in vivo interaction studies in female volunteers using omeprazole, simvastatin, or midazolam as marker substrate, a clinically relevant interaction of

drospirenone at doses of 3 mg 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).

Other forms of interaction

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, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range. Drospirenone causes an increase in plasma renin activity and plasma aldosterone induced by its mild antimineralocorticoid activity.

4.6 Fertility, 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.

Breastfeeding

Angeliq is not indicated during lactation.

4.7 Effects on ability to drive and use machines

Angeliq has no influence on the ability to drive and use machines.

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			Anemia
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

System Organ Class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)	Rare (< 1/1000)
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

Use of oestrogen-only or combined oestrogen-progestagen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see Section 4.4).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (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.

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 a 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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal

product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: progestogens and estrogens, combinations. ATC code: G03FA17

Estradiol

Angeliq contains synthetic 17ß-estradiol, which is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of oestrogen production in menopausal women, and alleviates menopausal symptoms. Oestrogens prevent bone loss following menopause or ovariectomy.

Drospirenone

Drospirenone is a synthetic progestogen.
As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestogen reduces, but does not eliminate the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.
Drospirenone displays aldosterone antagonist activity. Therefore, increases in sodium and water excretion and decreases in potassium excretion may be observed.
In animal studies, drospirenone has no oestrogenic, glucocorticoid or antiglucocorticoid activity.

Clinical trial information

- Relief of oestrogen-deficiency symptoms and bleeding patterns

Relief of menopausal symptoms was achieved during the first few weeks of treatment.
Amenorrhea was seen in 73% of the women during months 10-12 of treatment. Breakthrough bleeding and /or spotting appeared in 59% of the women during the first three months of treatment and in 27% during months 10-12 of treatment.

- Prevention of osteoporosis

  Oestrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass. The effect of oestrogen on the bone mineral density is dose-dependent. Protection appears to be effective as long as treatment is continued. After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women. Evidence from WHI trial and meta-analysed trials shows that current use of HRT, alone or in combination with a progestogen – given to predominantly healthy women – reduces the risk of hip, vertebral, and other osteoporotic fractures. HRT may also prevent fractures in women with low bone density and/or established osteoporosis, but the evidence for that is limited.
  After 2 years of treatment with Angeliq, the increase in hip bone mineral density (BMD) was 3.96 +/- 3.15% (mean +/- SD) in osteopenic patients and 2.78 +/- 1.89% (mean +/- SD) in non-osteopenic patients. The percentage of women who maintained or gained BMD in hip zone during treatment was 94.4% in osteopenic patients and 96.4% in non-osteopenic patients.
  Angeliq also had an effect on lumbar spine BMD. The increase after 2 years was 5.61 +/- 3.34% (mean +/- SD) in osteopenic women and 4.92+/- 3.02% (mean +/- SD) in non-osteopenic women. The percentage of osteopenic women who maintained or gained BMD in lumbar zone during treatment was 100% , whereas this percentage was 96.4% in non-osteopenic women.

- Antimineralocorticoid activity

  DRSP has aldosterone antagonistic properties that can result in a decrease in blood pressure in hypertensive women. In a double-blind placebo-controlled trial hypertensive postmenopausal women treated with Angeliq (n=123) for 8 weeks experienced a significant decrease in systolic/diastolic blood pressure values (office cuff versus baseline -12/-9 mm Hg, corrected for placebo effect -3/-4 mm Hg; 24h ambulatory blood pressure measurement versus baseline -5/--3 mm Hg, corrected for placebo effect -3/-2 mm Hg).
  Angeliq should not be used to treat hypertension. Women with hypertension should be treated according to hypertension guidelines.

5.2 Pharmacokinetic properties

Drospirenone

- Absorption

After oral administration drospirenone is rapidly and completely absorbed. With a single administration, peak serum levels of approx. 21.9 ng/ml are reached about 1 hour after ingestion. After repeated administration, a maximum steady-state concentration of 35.9 ng/ml is reached after about 10 days. The absolute bioavailability is between 76 and 85%. Concomitant ingestion of food had no influence on the bioavailability.

- Distribution

After oral administration, serum drospirenone levels decrease in two phases which are characterised by 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.

- Biotransformation

Drospirenone is extensively metabolized after oral administration. The major metabolites in plasma are the acid form of drospirenone, generated by opening of the lactone ring, and the 4,5-dihydro-drospirenone-3-sulphate, formed by reduction and subsequent sulfatation. Both major metabolites are pharmacologically inactive. Drospirenone is also subject to oxidative metabolism catalysed by CYP3A4.

- Elimination

The metabolic clearance rate of drospirenone in serum is 1.2-1.5 ml/min/kg showing an intersubject variability of about 25%. Drospirenone is excreted only in trace amounts in unchanged form. The metabolites of drospirenone are excreted with the faeces and urine at an excretion ratio 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

Following daily oral administration of Angeliq, drospirenone concentrations reached a steady-state after about 10 days. 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. At steady-state, mean serum levels of drospirenone fluctuate in the range of 14–36 ng/ml after administration of Angeliq. Pharmacokinetics of drospirenone are dose-proportional within the dose range of 1 to 4 mg.

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. The intake of food had no influence on the bioavailability of oestradiol as compared to drug intake on an empty stomach.

- Distribution

Following oral administration of Angeliq only gradually changing serum levels of oestradiol are observed within an administration interval of 24 hours. Because of the large circulating pool of oestrogen sulphates 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.

- Biotransformation

Oestradiol is rapidly metabolized, and besides oestrone and oestrone sulphate, 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. Oestrone reaches about 6-fold higher serum levels than oestradiol. The serum levels of the oestrone conjugates are about 26-times higher than the corresponding concentrations of free oestrone.

- Elimination

The metabolic clearance has been found to be about 30 ml/min/kg. The metabolites of oestradiol are excreted via urine and bile with a half-life of about 1 day.

- Steady-state conditions

Following daily oral administration of Angeliq, oestradiol concentrations reached a steady-state after about five days. Serum oestradiol levels accumulate approx. 2-fold. Orally administered oestradiol induces the formation of SHBG which influences the distribution with respect to the serum proteins, causing an increase of the SHBG-bound fraction and a decrease in the albumin-bound and unbound fraction indicating non-linearity of the pharmacokinetics of oestradiol after ingestion of Angeliq. 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.
Pharmacokinetics of oestradiol are dose-proportional at doses of 1 and 2 mg.

Special populations

- Hepatic impairment

The pharmacokinetics of a single oral dose of 3 mg DRSP in combination with 1 mg oestradiol (E2) 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 DRSP concentration-time profiles were comparable in both groups of women during the absorption/ distribution phases with similar Cmax and tmax 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 Impairment

The effect of renal insufficiency on the pharmacokinetics of DRSP (3 mg daily for 14 days) were investigated in female subjects with normal renal function and mild and moderate renal impairment. At steady-state of DRSP treatment, serum DRSP levels in the group with mild renal impairment (creatinine clearance CLcr, 50-80 ml/min) were comparable to those in the group with normal renal function (CLcr, > 80 ml/min). The serum DRSP levels were on average 37% higher in the group with moderate renal impairment (CLcr, 30-50 ml/min) compared to those in the group with normal renal function. Linear regression analysis of the DRSP AUC(0-24 hours) 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.

5.3 Preclinical safety data

Animal studies with estradiol and drospirenone have shown expected oestrogenic and gestagenic effects. There are no preclinical data of relevance to the prescriber that are additional to those already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate
Maize starch
Pregelatinised maize starch
Povidone
Magnesium stearate (E470b)

Film-coating material:
Hypromellose (E464)
Macrogol 6000
Talc (E553b)
Titanium dioxide (E171)
Ferric oxide, red (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Five years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Transparent polyvinyl film (250 µm) / aluminium foil (20 µm) blisters of 28 tablets with imprinted week days.
The pack sizes are 1x28 tablets and 3x28 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Bayer plc
400 South Oak Way

Reading
RG2 6AD

8 MARKETING AUTHORISATION NUMBER(S)

PL 00010/0518

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/12/2007

10 DATE OF REVISION OF THE TEXT

05/03/2018