

REGISTERED PACKAGE INSERT

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

ANGELIQ

Film-coated tablets

COMPOSITION

The pack contains 28 hormonal red film-coated tablets each with estradiol hemihydrate 1,033 mg (equivalent to estradiol 1,0 mg) and drospirenone 2,0 mg.

PHARMACOLOGICAL CLASSIFICATION

A. 21.8.2 Progesterones with estrogens.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Angeliq contains 17 β -estradiol, which is chemically and biologically identical to endogenous human estradiol, and the synthetic progestogen, drospirenone. 17 β -estradiol 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 estrogens.

- Effects of estradiol

Estrogen substitution.

- 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.

Antimineralocorticoid activity/antialdosterone activity

Drospirenone displays antimineralocorticoid activity (similar to progesterone and spironolactone) affecting the renin-angiotensin-aldosterone system.

Antiandrogenic activity

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.

Other properties

Drospirenone is devoid of estrogenic or thyrotropic activity.

Pharmacokinetic properties

- Estradiol

Absorption

Following oral administration, estradiol is completely absorbed. During absorption and first liver passage, estradiol undergoes extensive metabolism, thus reducing the absolute bioavailability of estrogen after oral administration to about 5% of the dose. Maximum concentrations of about 22 pg/ml were reached 6 to 8 hours after single oral administration of Angeliq. The intake of food had no influence on the bioavailability of estradiol as compared to drug intake on an empty stomach.

Distribution

Following oral administration of Angeliq only gradually changing serum levels of estradiol are observed within an administration interval of 24 hours. The terminal half-life of estradiol is in the range of about 13 to 20 hours after oral administration.

Estradiol is bound non-specifically to serum albumin and specifically to SHBG. Only about 1 to 2% of the circulating estradiol is present as free steroid, 40 to 45% is bound to SHBG. Orally administered estradiol 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 estradiol after ingestion of Angeliq. The apparent volume of distribution of estradiol after single intravenous administration is about 1 l/kg.

Metabolism

Estradiol is rapidly metabolised and, besides estrone and estrone sulphate, a large number of other metabolites and conjugates are formed. Estrone and estriol are known as pharmacologically active metabolites of estradiol; only estrone occurs in relevant concentrations in plasma. Estrone reaches about 6-fold higher serum levels than estradiol. The serum levels of the estrone conjugates are about 26 times higher than the corresponding concentrations of free estrone.

Elimination

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

Steady-state conditions

Following daily oral administration of Angeliq, estradiol concentrations reached a steady-state after about five days. Serum estradiol levels accumulate approximately 2-fold. With a dosing interval of 24 hours, mean steady-state serum levels of estradiol fluctuate in the range of 20 to 43 pg/ml following administration of Angeliq.

- Drospirenone

Absorption

Orally administered drospirenone is rapidly and almost completely absorbed. Maximum concentrations

of the drug in serum as indicated in the table below are reached about 1 hour after single and multiple ingestion of Angeliq. Pharmacokinetics of drospirenone are dose-proportional within the dose range of 1 to 4 mg. Bioavailability is between 76 and 85%. The intake of food had no influence on the bioavailability of drospirenone as compared to drug intake on an empty stomach.

Pharmacokinetic parameter	1 mg estradiol/ 1 mg drospirenone	Angeliq 2 mg *	1 mg estradiol/ 3 mg drospirenone
C _{max, sd} [ng/ml]	11,6	21,9	32,2
C _{max, ss} [ng/ml]	17,6	35,9	54,1
AUC(0-24h) _{sd} [ng/ml]	82,1	161	240
AUC(0-24h) _{ss} [ng/ml]	194	408	623

* Data for drospirenone 2 mg and drospirenone 3 mg were calculated by interpolation between the investigated doses of 1 mg drospirenone + 1 mg estradiol and 4 mg drospirenone + 1 mg estradiol.

C_{max}: Maximum concentration sd: single dose ss: steady-state

Distribution

After oral administration, serum drospirenone levels decrease in two phases with a mean terminal half-life of about 35 to 39 hours. Drospirenone is bound to serum albumin and does not bind to sex hormone binding globulin (SHBG) or corticoid binding globulin. Only 3 to 5% of the total serum drug concentrations are present as free steroid. The mean apparent volume of distribution of drospirenone is 3,7 to 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-sulphate, both of which are formed without involvement of the P450 system. Drospirenone is metabolised to a minor extent by cytochrome P450 3A4, based on *in vitro* data.

Elimination

The total clearance of drospirenone from serum is 1,2 to 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 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

During a treatment cycle, maximum steady-state concentrations of drospirenone in serum are reached as indicated in the table above. Steady-state conditions are reached after about 10 days of daily treatment with Angeliq. 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.

INDICATIONS

Hormone replacement therapy for the treatment of symptoms associated with the climacteric syndrome including vasomotor symptoms (such as hot flushes and sweating attacks), and atrophic urogenital conditions.

To reduce the risk of postmenopausal osteoporosis in women with an intact uterus.

CONTRA-INDICATIONS

Hormone replacement therapy should not be started in the presence of any of the conditions listed below. Should any of the conditions appear during hormone replacement therapy use, the product

should be stopped immediately.

- Abnormal vaginal bleeding of unknown causes.
- Known or suspected cancer of the breast.
- History of breast cancer.
- Known or suspected estrogen-dependent neoplasia.
- Presence or history of liver tumours (benign or malignant).
- Existing or previous serious hepatic diseases, if liver functions have not returned to normal.
- Presence or history of severe renal disease, as long as renal function values have not returned to normal.
- Evident active venous thrombosis (deep vein thrombosis, pulmonary embolism) or a history of these conditions.
- A previous history of repeated venous thromboembolism or known thrombophilia for which no anticoagulant treatment has yet been given.
- Severe hypertriglyceridaemia.
- Known or suspected pregnancy.
- Lactation.
- Known hypersensitivity to the active substances or to any of the excipients.

WARNINGS

Angeliq 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 hormone replacement therapy is started or continued.

Venous thromboembolism

Epidemiological studies have suggested that hormone replacement therapy is associated with a higher relative risk of developing venous thromboembolism, ie deep vein thrombosis or pulmonary embolism. The studies found a two to threefold higher risk for users compared with non-users, which for healthy women amounts to one to two additional cases of venous thromboembolism in 10 000 patient-years of treatment with hormone replacement therapy. The occurrence of such an event is more likely in the first year of hormone replacement therapy than later. Generally recognised risk factors for venous thromboembolism include a personal history or family history, severe obesity (Body Mass Index > 30 kg/m²) and systemic lupus erythematosus. There is no consensus about the role of varicose veins in venous thromboembolism.

Use of hormone replacement therapy in patients with a history of recurrent venous thromboembolism or known thrombophilic states already on anticoagulant treatment requires careful consideration of the benefit-risk of use of hormone replacement therapy (see "Contra-indications").

Personal or strong family history of recurrent thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a definite diagnosis has been made or anticoagulant treatment initiated, use of hormone replacement therapy in such patients should be viewed as contra-indicated. There are no clinical data regarding the use of Angeliq in patients on anticoagulant treatment.

The risk of venous thromboembolism may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all post-operative patients, scrupulous attention should be given to prophylactic measures to prevent venous thromboembolism following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping hormone replacement therapy four to six weeks earlier, if possible.

If venous thromboembolism develops or is suspected after initiating therapy, the drug should be discontinued.

Patients should be told to contact their doctors immediately if they become aware of a potential thromboembolic symptom (eg painful swelling of a leg, sudden pain in the chest, dyspnoea).

Breast cancer

A meta-analysis from 51 epidemiological studies reported that there is a modest increase in the risk of having breast cancer diagnosed in women who have used hormone replacement therapy for more than five years. The findings may be due to an earlier diagnosis, the biological effects of hormone replacement therapy, 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 cessation of hormone replacement therapy. Breast cancers diagnosed in current or recent users of hormone replacement therapy are less likely to have spread outside the breast than those found in non-users.

Endometrial cancer

Prolonged exposure to unopposed estrogens increases the risk of the development of endometrial carcinoma. The addition of drospirenone opposes the development of endometrial hyperplasia caused by estrogens. Nevertheless, clinical surveillance of menopausal women receiving hormone replacement therapy is essential. Persistent breakthrough bleeding during treatment may be an indication for endometrial assessment, which may include biopsy.

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 hormone replacement therapy 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.

Gallbladder disease

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

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 hormone replacement therapy use and the development of clinical hypertension has not been established. Small increases in blood pressure have been reported in women taking hormone replacement therapy; clinically relevant increases are rare. However, if in individual cases a sustained clinically significant hypertension develops during the use of hormone replacement therapy, then withdrawing the hormone replacement therapy 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 hyperkalaemia 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 hyperbilirubinemias 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 hormone replacement therapy 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 hormone replacement therapy.

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

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

Certain patients may develop undesirable manifestations of estrogenic stimulation under hormone replacement therapy, 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 estrogens. 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 hormone replacement therapy.

The following conditions have been reported to occur or deteriorate with hormone replacement therapy use. Although the evidence of an association with hormone replacement therapy use is inconclusive, women with these conditions and treated with hormone replacement therapy should be carefully monitored.

- epilepsy
- benign breast disease
- asthma
- migraine
- porphyria
- otosclerosis
- systemic lupus erythematosus
- chorea minor

INTERACTIONS

Effects of other medicines on Angeliq

An increased clearance of sex hormones due to hepatic enzyme induction may reduce the clinical efficacy of the drug and eventually cause irregular bleeding. Such hepatic enzyme-inducing properties have been established for hydantoins, barbiturates, primidone, carbamazepine and rifampicin, and are also suspected for oxcarbazepine, topiramate, felbamate and griseofulvin. The mechanism of this interaction appears to be based on the hepatic enzyme-inducing properties of these drugs. Maximal enzyme induction is generally not seen for 2 to 3 weeks, but may then be sustained for at least 4 weeks after the cessation of drug therapy.

In rare cases reduced estradiol levels have been observed under the simultaneous use of certain antibiotics (eg penicillins and tetracycline).

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. Nevertheless, inhibitors of CYP3A4, like cimetidine, ketoconazole and others, may inhibit the metabolism of estradiol.

Acute alcohol ingestion during use of hormone replacement therapy may lead to elevations of circulating estradiol levels.

Interaction of Angeliq with other medicines

Based on *in vitro* inhibition studies and on an *in vivo* interaction study in female volunteers using omeprazole as marker substrate, drospirenone shows little propensity to interact with the metabolism of other drugs.

Pharmacodynamic interaction with antihypertensive medicines

Interactions of Angeliq with antihypertensive medicines were not investigated; therefore, potential synergistic effects cannot be excluded.

The effects of concomitant intake of estradiol/drospirenone (3 mg) on blood pressure and electrolyte balance has been investigated in patients treated with an ACE inhibitor (enalapril). There was a slight decrease in the mean baseline-adjusted 24 hour blood pressure in the estradiol/drospirenone group relative to the placebo group.

Estrogen and estrogen/progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke. Should any of these occur or be suspected, estrogens should be discontinued immediately.

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, eg 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.

PREGNANCY AND LACTATION

Angeliq should not be used during pregnancy and lactation. If pregnancy occurs during medication with Angeliq, treatment should be discontinued promptly. No clinical data on exposed pregnancies are available for Angeliq. Animal studies have shown adverse effects during pregnancy and lactation. The potential risk for humans is unknown. The results of epidemiological studies to date have not indicated a teratogenic effect when pregnant women were inadvertently exposed to estrogen/progestogen combinations.

Small amounts of drospirenone are excreted with the milk.

DOSAGE AND DIRECTIONS FOR USE**How to start Angeliq**

Women who do not take estrogens or women who change from a continuous combination product may start treatment at any time. Patients changing from a sequential combined hormone replacement therapy should start treatment 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. 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, bleeding may occur.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Side-effects

Serious undesirable effects associated with the use of hormone replacement therapy are also mentioned in "Warnings".

The table below attributes frequencies to the undesirable effects of Angeliq. 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 treatment with 1 mg estradiol in combination with 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 "Effects of drospirenone" under "Pharmacological action"). 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.

Organ system	Common ($\geq 1/100$, $< 1/10$)	Uncommon ($\geq 1/1000$, $< 1/100$)
Body as a whole	Abdominal pain or bloating, asthenia, pain in extremity.	Pain in back or pelvis, chills, malaise, laboratory test abnormal.
Cardiovascular system	-	Migraine, hypertension, chest pain, palpitation, varicose veins, venous thrombosis, superficial thrombophlebitis, vasodilatation.
Digestive	Nausea.	Gastrointestinal disorder, increased appetite, liver function test abnormal.
Metabolic and nutritional	-	Generalised or localised oedema, weight gain, hyperlipemia.
Musculoskeletal system	-	Muscle cramps, arthralgia.
Nervous system	Headache, mood swings, hot flushes, nervousness.	Insomnia, dizziness, libido decreased, concentration ability impaired, paraesthesia, sweating increased, anxiety, dry mouth, vertigo.
Respiratory system	-	Dyspnoea.
Skin and appendages	Benign breast neoplasms, breast enlargement.	Alopecia, skin or hair disorder, hirsutism, breast carcinoma, breast engorgement.
Special senses	-	Taste disturbance.
Urogenital	Uterine fibroids enlarged, cervix neoplasm, leukorrhoea.	Vulvovaginitis, endometrial or cervical disorder, bleeding, dysmenorrhoea, ovarian cyst, urinary tract infections or incontinence.

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

Special precautions

Medical examination/consultation

Before initiating or reinstating hormone replacement therapy, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contra-indications 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 should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual. A careful appraisal of the risks and benefits should be undertaken over time in women treated with hormone replacement therapy.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Acute toxicity studies indicate that, even in the case of inadvertent intake of a multiple of the therapeutic dose, no acute toxicity risk is to be expected. In clinical studies up to 100 mg of drospirenone and estrogen/progestogen preparations containing 4 mg of estradiol 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.

IDENTIFICATION

Medium red, round film-coated tablets with convex faces, one side embossed with the letters DL in a regular hexagon.

PRESENTATION

Cartons containing 1 or 3 PVC/aluminium blisters with 28 tablets.

STORAGE INSTRUCTIONS

Store below 30°C. Keep out of reach of children.

REGISTRATION NUMBER

37/21.8.2/0451

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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