SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ANGELIQ
Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains sugar (48,2 mg lactose monohydrate per tablet).
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1. Therapeutic 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.

4.2. Posology and method of administration

Posology

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

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.

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.

Missed tablets

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.

Special populations

Paediatric patients

ANGELIQ is not indicated for use in children and adolescents.

Geriatric patients

There is no data suggesting a need for dosage adjustment in elderly patients. In women aged 65 years and 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). ANGELIQ is contraindicated in women with presence or history of liver tumours and with severe hepatic disease (see section 4.3). For women with impaired liver function, close supervision is needed and in case of deterioration of markers of liver function, use of HRT should be stopped (see section 4.4).

Patients with renal impairment

In women with mild to 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

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.

- Known hypersensitivity to the active substances or to any of the excipients (see section 6.1)
- Abnormal vaginal bleeding of unknown causes
- Known or suspected cancer of the breast
- Personal and family 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
- Acute arterial thromboembolism (e.g. myocardial infarction, stroke)
- 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
- A high risk of venous or arterial thrombosis

- Severe hypertriglyceridaemia
- Known or suspected pregnancy (see section 4.6)
- Lactation (see section 4.6)
- Inherited thrombophilia .
- Patients known with inherited genetic mutations: BRCA1 and BRCA 2 genes.
- Early menstrual periods (before the age of 12 years).
- History of non-cancerous breast diseases (atypical hyperplasia or lobular carcinoma in situ).
- Previous treatment using radiation therapy to the chest or breast.
- Previous exposure to diethylstilbestrol (DES).

4.4. Special warnings and precautions for use

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.

During ANGELIQ use, therapy should be discontinued immediately in case a contraindication is discovered, as well as in the following situations:

- Migrainous or frequent and unusually severe headaches that occur for the first time or other symptoms that are possible prodroma of cerebrovascular occlusion.
- Recurrence of cholestatic jaundice or cholestatic pruritus which occurred first during pregnancy or previous use of sex steroids.
- Symptoms of a thrombotic event or suspicion thereof.

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. ANGELIQ should not be prescribed in case of a negative risk benefit assessment.

Venous thromboembolism

Epidemiological studies have suggested that hormone replacement therapy is associated with a higher relative risk of developing venous thromboembolism, i.e. 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/m^2) 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 section 4.3).

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 contraindicated. 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 medicine should be discontinued.

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

Arterial thromboembolism

Two large clinical trials with continuous combined conjugated equine estrogens and medroxyprogesterone acetate showed a possible increased risk of coronary heart disease in the first year of use and no benefit thereafter. One large clinical trial with conjugated equine estrogens alone showed a potential reduction of coronary heart disease 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 conjugated equine estrogens alone or combined with medroxyprogesterone acetate a 30-40 % increased risk of stroke was found. It is uncertain whether these findings also extends to other hormone replacement therapy products, such as ANGELIQ or non-oral routes of administration.

Tumours

Breast cancer

ANGELIQ contains (estrogen and progestogen or estrogen only) which, on prolonged use, may increase the risk of developing breast cancer. A meta-analysis of prospective epidemiological studies from 1992 to 2018 reported a significant increase in the risk of developing breast cancer in 55 575 women 40-59 years of age who used menopausal hormone therapy (MHT). The risk increased steadily with duration of use and was slightly greater for estrogen-progestogen than estrogen only preparations, and the risk persisted for more than 10 years after stopping the treatment. The relative risk (RR) to develop breast cancer for estrogen-progestogen preparations was 1,60 at 1-4 years and RR=2,08 at 5-14 years, while that for estrogen only preparations were 1,17 at 1-4 years and 1,33 at 5-14 years. There was no risk to develop breast cancer in women who started MHT at 60 years of age.
All women on ANGELIQ should receive yearly breast examinations by a healthcare provider and perform monthly breast self- examinations. Mammography evaluations should be done based on patient age, risk factors, and prior mammogram results.

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 estrogen-only or combined estrogen-progestogen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.

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

Endometrial cancer

Prolonged exposure to unopposed estrogens increases the risk of the development of endometrial hyperplasia or 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.

Dementia

There is limited evidence from clinical studies with conjugated equine estrogens-containing preparations 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 the early menopause, as observed in other studies. It is unknown whether these findings also extend to other hormone replacement therapy products such as ANGELIQ.

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.

ANGELIQ has the potential to lower blood pressure in women with elevated blood pressure. In normotensive women, relevant changes in blood pressure are not expected.

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 medicines.

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

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

Depressed mood and depression are well-known undesirable effects of hormonal containing products (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their medical practitioner in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Each tablet contains 48,2 mg lactose monohydrate. 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.

Medical examination/consultation

Before initiating or reinstituting 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 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 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.

4.5. Interactions with other medicines and other forms of interaction.

Effects of other medicines on ANGELIQ

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. 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 therapy enzyme induction may be sustained for about 4 weeks.

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.

Substances with variable effects on the clearance of sex hormones:
When co-administered with sex hormones, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of estrogen 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. fluconazole, itraconazole, ketoconazole, voriconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the progestin or the estrogen or both.

In a multiple dose study with a drospirenone (3 mg/day) / estradiol (1,5 mg/day) combination, coadministration 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 estradiol, although the AUC(0-24h) of its less potent metabolite estrone increased 1,39-fold (90 %CI: 1,27, 1,52).

Interaction with alcohol

Acute alcohol ingestion during use of ANGELIQ may lead to elevations of circulating estradiol levels.

Interaction of ANGELIQ with other medicines

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 substrates, a clinically relevant interaction of drospirenone at doses of 3 mg with the cytochrome P450 enzyme mediated metabolism of other medicines in unlikely.

Pharmacodynamic interaction with antihypertensive medicines and non-steroidal anti-inflammatory drugs (NSAIDs)

Hypertensive women treated with ANGELIQ and anti-hypertensive medicines, e.g. ACE inhibitors, angiotensin-II-receptor antagonists, and hydrochlorthiazide may experience an additional decrease in blood pressure.

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.

Combined use of ANGELIQ and NSAIDs or antihypertensive medicines is unlikely to increase serum potassium. Concomitant use of these three types of medicines together may cause a small increase in serum potassium, more pronounced in diabetic women.

Other forms of interactions

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.

4.6. Pregnancy and lactation

ANGELIQ should not be used during pregnancy and lactation.

Pregnancy
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.

Lactation
Small amounts of drospirenone are excreted with the milk.

4.7. Effects on ability to drive and use machines

No studies on the ability to drive and use machines have been performed. No effects on the ability to drive and use machines have been observed in users of ANGELIQ.

4.8. Undesirable effects

Summary of safety profile

Serious undesirable effects associated with the use of hormone replacement therapy are also mentioned in section 4.4.

The most commonly reported adverse drug reaction (ADR) with ANGELIQ are breast pain, female genital tract bleeding and gastrointestinal and abdominal pains. They occur in ≥ 6 % of users.

During the first few months of treatment, bleeding and spotting can occur. These are usually temporary and normally disappear after continued treatment (see section 5.1). The frequency of bleeding decreases with the duration of treatment.

Tabulated summary of adverse reactions

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 13 phase II and phase III clinical studies (n = 2 842 women at risk) and considered at least possibly related to treatment with 1 mg estradiol in combination with 1, 2, or 3 mg drospirenone.

Within each frequency grouping, ADRs are presented in order of decreasing seriousness.
Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100) and rare (≥ 1/10 000 to < 1/1 000).

Organ system	Very Common	Common	Uncommon	Rare
Psychiatric disorders	-	Emotional lability	-	-
Nervous system disorders	-	Migraine	-	-
Vascular disorders	-	-	Venous and arterial thromboembolic events *	-
Gastrointestinal disorders	-	Gastrointestinal and abdominal pains	-	-
Reproductive system and breast disorders	Breast pain *** Female genital tract bleeding	Cervical polyp	Breast cancer **	-

Adverse events in clinical studies were coded using the MedDRA dictionary (version 13.0). Different MedDRA terms representing the same medicinal phenomenon have been grouped together as single adverse reactions to avoid diluting or obscuring the true effect.

* Evidence for relatedness and estimated frequency derived from epidemiological studies with ANGELIQ (EURAS HRT). 'Venous and arterial thromboembolic events' summarises the following Medical Labelling Groupings: Peripheral deep venous occlusion, thrombosis and embolism/pulmonary vascular occlusion, thrombosis, embolism and infarction/myocardial infarction/cerebral infarction and stroke not specified as haemorrhagic

** Evidence for relatedness derived from post-marketing experience; frequency estimation derived from clinical studies with ANGELIQ.

*** Including breast discomfort

For venous and arterial thromboembolic events, breast cancer and migraine see also sections 4.3 and 4.4.

Description of selected adverse reactions

Adverse reactions with very low frequency or with delayed onset of symptoms which are considered to be related to the group of continuous combined products for hormone replacement therapy are listed below (see also section 4.4):

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)
- Ovarian cancer: Use of estrogen-only or combined estrogen-progestogen 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.

Other conditions

- Gallbladder disease (estrogens are known to increase the lithogenicity of the bile)
- Dementia (there is limited evidence from clinical studies with conjugated equine estradiol-containing preparations that hormonal treatment may increase the risk of probable dementia if initiated in women aged 65 years or older. The risk may be decreased if treatment is initiated in the early menopause, as observed in other studies. It is unknown whether these findings also extend to other hormone replacement therapy products.)
- Endometrial cancer (studies have suggested that the appropriate addition of progestogens eliminates the increase in risk resulting from the use of unopposed estrogen)
- Hypertension (ANGELIQ has the potential to lower blood pressure in women with elevated blood pressure)
- Disturbances of liver function
- Hypertriglyceridaemia (increased risk of pancreatitis when using hormone replacement therapy)
- 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 hormone replacement therapy is not conclusive: epilepsy; benign breast disease; asthma; porphyria; systemic lupus erythematosus; otosclerosis; chorea minor
- In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema
- Hypersensitivity (incl. symptoms such as rash and urticaria)
- In exceptional cases erythema nodosum, erythema multiforme, chloasma and haemorrhagic dermatitis have been reported in women receiving hormone replacement therapy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form",** found online under SAHPRA's publications: http://www.sahpra.org.za/Publications/index/8

4.9. Overdose

Acute toxicity studies did not indicate a risk of acute adverse effects in case of inadvertent intake of a multiple of the daily therapeutic dose. In clinical studies up to 100 mg of drospirenone and

estrogen/progestogen preparations containing 4 mg of estradiol were well tolerated.
Overdosage may cause nausea and vomiting and withdrawal bleeding may occur in some women. There is no specific antidote andtreatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC Code: G03FA17
Pharmacotherapeutic group: progestogens and oestrogens, combinations

ANGELIQ contains 17ß-estradiol, which is chemically and biologically identical to endogenous human estradiol, and the synthetic progestogen, drospirenone. 17ß-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.

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

Distribution

Following oral administration, 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. 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, 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.

Drospirenone

Absorption

Orally administered drospirenone is rapidly and almost completely absorbed. Maximum concentrations in serum as indicated in the table below are reached about 1 hour after single and multiple ingestion. 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 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 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 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. Drospirenone is also subject to oxidative metabolism catalysed by CYP3A4.

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. 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.

5.3. Preclinical safety data

Not Applicable

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

- Ferric oxide red
- Hypromellose 5cP
- Lactose monohydrate
- Magnesium stearate
- Maize starch
- Polyethylene glycol
- Povidone
- Pregelatinised starch

- Talc
- Titanium dioxide

6.2. Incompatibilities

None.

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store at or below 30 °C.

6.5. Nature and contents of container

PVC/aluminium blisters with 28 tablets.
Pack sizes of 28 and 84 tablets. Not all pack sizes may be marketed.

6.6. Special precautions for disposal

Not applicable

7. HOLDER OF CERTIFICATE OF REGISTRATION

Bayer (Pty) Ltd
Reg. No.: 1968/011192/07
27 Wrench Road
Isando
1609

8. REGISTRATION NUMBER

37/21.8.2/0451

9. DATE OF FIRST AUTHORISATION

28 May 2004

10. DATE OF REVISION OF THE TEXT

25 October 2024

Botswana: (S2) BOT0901586
Namibia: NS2 04/21.8.2/1455