Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Allurene 1 mg/2 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains: 1 mg estradiol (as estradiol hemihydrate) and 2 mg drospirenone.
Excipient: 46 mg lactose.
For a 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.

Dosage
One tablet is taken daily. Each blister 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, 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.

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 idiopathic 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
- Porphyria
- Severe renal insufficiency or acute renal failure
- Known hypersensitivity to the active substances or to any of the excipients

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

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 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 Allurene, in particular:

- Leiomyoma (uterine fibroids) or endometriosis,
- A history of, or risk factors for, thromboembolic disorders (see below
- Risk factors for oestrogen dependent tumours, e.g. 1 st degree heredity for breast cancer
- Hypertension
- Liver disorders (eg 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

The risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods *(see section 4.8).* The addition of a progestogen for at least 12 days per cycle in non-hysterectomised women greatly reduces this risk.

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

A randomised placebo-controlled trial**;** the Women's Health Initiative study (WHI), and epidemiological studies, including the Million Women Study (MWS), have reported an increased risk of breast cancer in women taking oestrogens**,** oestrogen-progestogen combinations or tibolone for HRT for several years *(see Section 4.8).* For all HRT, an excess risk becomes apparent within a few years of use and increases with duration of intake but returns to baseline within a few (at most five) years after stopping treatment.

In the MWS, the relative risk of breast cancer with conjugated equine oestrogens (CEE) or estradiol (E2) was greater when a progestogen was added, either sequentially or continuously, and regardless of type of progestogen. There was no evidence of a difference in risk between the different routes of administration.

In the WHI study, the continuous combined conjugated equine oestrogen and medroxyprogesterone acetate (CEE + MPA) product used was associated with breast cancers that were slightly larger in size and more frequently had local lymph node metastases compared to placebo.

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

Venous thromboembolism

HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. One randomised controlled trial and epidemiological studies found a two- to threefold higher risk for users compared with non-users.**-**For non-users it is estimated that the number of cases of VTE that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged between 60 –69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE over a 5 year period will be between 2 and 6 (best estimate=4) per 1000 women aged 50-59 years and between 5 and 15 (best estimate =9) per 1000 women aged 60-69 years. The occurrence of such an event is more likely in the first year of HRT than later.

Generally recognised risk factors for VTE include a personal history or family history, severe obesity (BMI > 30 kg/m 2) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE.

Patients with a history of VTE or known thrombophilic states have an increased risk of VTE.

HRT may add to this risk. Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all postoperative patients, scrupulous attention should be given to prophylactic measures to prevent VTE 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 HRT 4 to 6 weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilised.

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 (eg, painful swelling of a leg, sudden pain in the chest, dyspnea).

Coronary artery disease (CAD)
There is no evidence from randomised controlled trials of cardiovascular benefit with continuous combined conjugated oestrogens and medroxyprogesterone acetate (MPA). Two large clinical trials (WHI and HERS i.e. Heart and Estrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT products there are only limited data from randomised controlled trials examining effects in cardiovascular morbidity or mortality. Therefore, it is uncertain whether these findings also extend to other HRT products.

Stroke
One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined conjugated oestrogens and MPA. For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 11 per 1000 women aged 60-69 years. It is estimated that for women who use conjugated estrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate = 1) per 1000 users aged 50-59 years and between 1 and 9 (best estimate = 4) per 1000 users aged 60-69 years. It is unknown whether the increased risk also extends to other HRT products.

Ovarian cancer
Long-term (at least 5-10 years) use of oestrogen-only HRT products in hysterectomised women has been associated with an increased risk of ovarian cancer in some epidemiological studies. It is uncertain whether long-term use of combined HRT confers a different risk than oestrogen-only products

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.

Estrogens 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).
There is no conclusive evidence for improvement of cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined CEE and MPA after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products.
The progestin component in Allurene 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 Allurene due to the aldosterone antagonist activity of drospirenone *(see section 5.1).* Allurene should not be used to treat hypertension. Women with hypertension should be treated according to Hypertension Guidelines.
Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking HRT.
Each tablet of this medicinal product contains 46 mg lactose per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose-free diet should take this amount into consideration.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on Allurene
The metabolism of oestrogens [and progestogens] may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamezapine) and anti- infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).
Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St John's Wort (Hypericum Perforatum) may induce the metabolism of oestrogens [and progestogens].

Clinically, an increased metabolism of oestrogens and progestogens may lead to decreased effect and changes in the uterine bleeding profile.
The main metabolites of drospirenone are generated without involvement of the cytochrome P450 system. Inhibitors of this enzyme system are therefore unlikely to influence the metabolism of drospirenone.

Interaction of Allurene with other medicinal products
Based on *in vitro* inhibition studies and on *in vivo* interaction studies in female volunteers receiving steady-state doses of 3 mg drospirenone per day and omeprazole, simvastatin, or midazolam as marker substrate, a clinically relevant interaction of drospirenone with the cytochrome P450 enzyme mediated metabolism of other drugs is unlikely.
Concomitant use of Allurene 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 Allurene and antihypertensive medications may experience an additional decrease in blood pressure *(see section 4.4).*

4.6 Pregnancy and lactation

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

Lactation
Allurene is not indicated during lactation.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The table below reports adverse reactions by MedDRA system organ classes (MedDRA SOCs). The frequencies are based on clinical trial data. The adverse reactions were recorded in 7 phase III clinical studies (n = 2424 women) and considered as at least possibly causally related to Allurene (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 Effects of drospirenone).* 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		Dyspnea	
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, Galactorrhea

General disorders and administration site conditions	Asthenia, Localized edema	Generalized edema, 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 Allurene 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.
According to evidence from a large number of epidemiological studies and one randomised placebo-controlled trial, the Women's Health Initiative (WHI), the overall risk of breast cancer increases with increasing duration of HRT use in current or recent HRT users.
For *oestrogen-only* HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which >80% of HRT use was oestrogen-only HRT) and from the epidemiological Million Women Study (MWS) are similar at 1.35 (95%CI 1.21 – 1.49) and 1.30 (95%CI 1.21 – 1.40), respectively.
For *oestrogen plus progestogen* combined HRT, several epidemiological studies have reported an overall higher risk for breast cancer than with oestrogens alone.
The MWS reported that, compared to never users, the use of various types of oestrogen-progestogen combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95%CI: 1.88 – 2.12) than use of oestrogens alone (RR = 1.30, 95%CI: 1.21 – 1.40) or use of tibolone (RR=1.45; 95%CI 1.25-1.68).
The WHI trial reported a risk estimate of 1.24 (95%CI 1.01 – 1.54) after 5.6 years of use of oestrogen-progestogen combined HRT (CEE + MPA) in all users compared with placebo.

The absolute risks calculated from the MWS and the WHI trial are presented below:
The MWS has estimated, from the known average incidence of breast cancer in developed countries, that:

- For women not using HRT, about 32 in every 1000 are expected to have breast cancer diagnosed between the ages of 50 and 64 years.
- For 1000 current or recent users of HRT, the number of additional cases during the corresponding period will be

- For users of oestrogen-only replacement therapy
  - between 0 and 3 (best estimate = 1.5) for 5 years' use
  - between 3 and 7 (best estimate = 5) for 10 years' use.

- For users of oestrogen plus progestogen combined HRT,
  - between 5 and 7 (best estimate = 6) for 5 years' use
  - between 18 and 20 (best estimate = 19) for 10 years' use.

The WHI trial estimated that after 5.6 years of follow-up of women between the ages of 50 and 79 years, an *additional* 8 cases of invasive breast cancer would be due to *oestrogen-progestogen combined* HRT (CEE + MPA) per 10,000 women years.

According to calculations from the trial data, it is estimated that:

For 1000 women in the placebo group,
- about 16 cases of invasive breast cancer would be diagnosed in 5 years.

For 1000 women who used oestrogen + progestogen combined HRT (CEE + MPA), the number of additional cases would be
- between 0 and 9 (best estimate = 4) for 5 years' use.

The number of additional cases of breast cancer in women who use HRT is broadly similar for women who start HRT irrespective of age at start of use (between the ages of 45-65) *(see section 4.4).'*
Endometrial cancer
In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed oestrogens. According to data from epidemiological studies, the best estimate of the risk is that for women not using HRT, about 5 in every 1000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65. Depending on the duration of treatment and oestrogen dose, the reported increase in endometrial cancer risk among unopposed oestrogen users varies from 2-to 12-fold greater compared with non-users. Adding a progestagen to oestrogen-only therapy greatly reduces this increased risk.
Other adverse reactions have been reported in association with oestrogen/progestogen treatment:
- Oestrogen-dependent neoplasms benign and malignant, e.g. endometrial cancer.
- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone replacement therapy users than among non-users. For further information, see section 4.3 Contraindications and 4.4 Special warnings and precautions for use.
- Myocardial infarction and stroke
- Gall bladder disease.
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.
- Probable dementia *(see section 4.4)*

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Progestogens and estrogens, combinations; ATC code G03F A

Estradiol
Allurene 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 estrogenic, 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 Allurene, 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.
  Allurene 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 Allurene (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).
  Allurene 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 h. Drospirenone is bound to serum albumin and does not bind to sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG). Only 3 - 5 % of the total serum drug concentrations are present as free steroid. The mean apparent volume of distribution of drospirenone is 3.7 - 4.2 l/kg.

Metabolism
Drospirenone is extensively metabolized after oral administration. The major metabolites in the plasma are the acid form of drospirenone, generated by opening of the lactone ring, and the 4,5-dihydro-drospirenone-3-sulfate, both of which are formed without involvement of the P450 system. Both major metabolites are pharmacologically inactive. Drospirenone is metabolized to a minor extent by cytochrome P450 3A4 based on *in vitro* data. In vitro and clinical studies do not indicate an inhibitory effect of DRSP on CYP enzymes after administration of Allurene.

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 feces and urine at an excretion ratio of about 1.2 to 1.4. The half-life of metabolite excretion with the urine and feces is about 40 h.

Steady-state conditions and linearity
Following daily oral administration of Allurene, 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 Allurene. Pharmacokinetics of drospirenone are dose-proportional within the dose range of 1 to 4 mg.

Estradiol

Absorption
Following oral administration, estradiol is rapidly and completely absorbed**.** During the absorption and the 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 6-8 h after single oral administration of Allurene. 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 Allurene only gradually changing serum levels of estradiol are observed within an administration interval of 24 hours. Because of the large circulating pool of estrogen sulfates and glucuronides on the one hand and the enterohepatic recirculation on the other hand, the terminal half-life of estradiol represents a composite parameter that is dependent on all of these processes and is in the range of about 13-20 h after oral administration.
Estradiol is bound non-specifically to serum albumin and specifically to SHBG. Only about 1-2 % of the circulating estradiol is present as free steroid, 40-45 % is bound to SHBG. The apparent volume of distribution of estradiol after single intravenous administration is about 1 l/kg.

Metabolism
Estradiol is rapidly metabolized, and besides estrone and estrone sulfate, 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 Allurene, estradiol concentrations reached a steady-state after about five days. Serum estradiol levels accumulate approx. 2-fold. 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 Allurene. With a dosing interval of 24 hours, mean steady-state serum levels of estradiol fluctuate in the range of 20-43 pg/ml following administration of Allurene. Pharmacokinetics of Estradiol 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 estradiol (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 (0-24h) values in relation to the creatinine clearance revealed a 3.5 % increase with a 10 ml/min reduction of creatinine clearance. This slight increase is not expected to be of clinical relevance.

5.3 Preclinical safety data

Animal studies with estradiol and drospirenone have shown expected estrogenic 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

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

No special precautions for storage

6.5 Nature and contents of container

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

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 MARKETING AUTHORISATION HOLDER

Bayer Limited
The Atrium
Blackthorn Road
Dublin 18

8 MARKETING AUTHORISATION NUMBER

PA 1410/014/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 March 2004

Date of last renewal: 11 December 2007

10 DATE OF REVISION OF THE TEXT

May 2008