Summary of product characteristics

Estradiol Valeraat 1 mg / Dienogest 2 mg Laboratorios Léon Farma, filmomhulde tabletten

estradiol valerate / dienogest

1. NAME OF THE MEDICINAL PRODUCT

Estradiol Valeraat 1 mg / Dienogest 2 mg Laboratorios Léon Farma, filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains: estradiol valerate 1.0 mg (equivalent to 0.764 mg estradiol) and dienogest 2.0 mg

Excipients with know effect: each tablet contains 58.22 mg of lactose monohydrate.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Tablets are light pink and rounded with a diameter of 6 mm approx.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone replacement therapy (HRT) for estrogen deficiency symptoms in postmenopausal women more than one year post menopause.

Experience of treating women older than 65 years is limited.

4.2 Posology and method of administration

Posology

How to start <**invented name**> 1 mg/2 mg

Women who do not take hormone replacement therapy (HRT) or women who change from another continuous combined HRT product may start treatment at any time.

Women changing from a continuous sequential HRT regimen should begin the day following completion of the prior regimen.

Women changing from a cyclic HRT regimen should begin the day after the treatment-free period.

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

Method of ~~A~~administration

For oral use.

The tablets are to be swallowed whole with some liquid. 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. In case 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.
For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also Section 4.4) should be used.

Additional information on special populations

Paediatric patients
<invented name> is not indicated for use in children and adolescents.

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

Patients with hepatic impairment
<invented name> has not been specifically studied in patients with hepatic impairment. <invented name> is contraindicated in women with severe hepatic diseases (see section 4.3).

Patients with renal impairment
<invented name> has not been specifically studied in renally impaired patients. Available data do not suggest a need for dosage adjustment in this patient population.

4.3 Contraindications

- Known, past or suspected breast cancer;
- Known or suspected estrogen-dependent malignant tumours (e.g. endometrial cancer);
- Undiagnosed genital bleeding;
- Untreated endometrial hyperplasia;
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism);
- Know thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4);
- 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;
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1;
- Porphyria

4.4 Special warnings and precautions for use

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

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

Medical examination/follow-up

Before initiating or reinstituting 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 (see 'Breast cancer' below). Investigations, including appropriate imaging tools, e.g. mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need supervision

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

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for, thromboembolic disorders (see below)
- Risk factors for estrogen dependent tumours, e.g. 1st degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus.
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

Reasons for immediate withdrawal of therapy:

Therapy should be discontinued in case a contra**i**ndication is discovered and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache
- Pregnancy

Endometrial hyperplasia and carcinoma

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

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

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

Breast cancer

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

Combined oestrogen-progestagen therapy

A randomised placebo-controlled trial the Women's Health Initiative study (WHI), and a metanalysis of prospective epidemiological studies, are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestagen for HRT that becomes apparent after about 3 (1-4) years (see Section 4.8).

Oestrogen-only therapy

The WHI trial found no increase in the risk of breast cancer in hysterectomised women using oestrogen-only HRT. Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is lower than that found in users of oestrogen-progestagen combinations (see section 4.8).

Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.

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

Ovarian cancer

Ovarian cancer is much rarer than breast cancer.

Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only or combined oestrogen-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 use of combined HRTs may be associated with a similar or slightly smaller risk (see Section 4.8).

Venous thromboembolism

- HRT is associated with a 1.3-3 fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later. (see section 4.8)
- Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3)
- Generally recognised risk factors for VTE include, use of oestrogens, older age, major surgery, prolonged immobilization, obesity (BMI > 30 kg/m2), pregnancy/postpartum period, systemic lupus erythematosus (SLE) and cancer. There is no consensus about the possible role of varicose veins in VTE.

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

- In women with no personal history of VTE but with a first degree relative with a history of

thrombosis at young age, screening may be offered after careful counseling regarding its limitations (only a proportion of thrombophilic defects are identified by screening).

If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is "severe" (e.g, antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated.

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

- If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (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 protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestagen or oestrogen-only HRT.

Combined oestrogen-progestogen therapy

The relative risk of CAD during use of combined oestrogen+progestogen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to oestrogen+progestogen use is very low in healthy women close to menopause, but will rise with more advanced age.

Oestrogen-only

Randomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy.

Ischaemic stroke

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

Other conditions

Estrogens may cause fluid retention, and therefore, patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients of estradiol valerate and dienogest is increased.

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

- Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.
- Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex- hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are

unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I- antitrypsin, ceruloplasmin).

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

ALT elevations

During clinical trials with patients treated for hepatitis C virus (HCV) infections with the combination regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with and without ribavirin, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Additionally, also in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the following combination drug regimens ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir. See section 4.5

Warnings about excipients

The tablet contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

Effects of other medicinal products on <invented name>

Substances increasing the clearance of sex hormones (reduced efficacy due to enzyme induction), e-g.:

The metabolism of estrogen and dienogest may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. barbiturates, phenytoin, primidone, carbamezapin) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz) and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and products containing the herbal remedy St. John's Wort (hypericum perforatum)

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

Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After cessation of drug therapy, the enzyme induction may be sustained for about 4 weeks.

Substances with variable effects on the clearance of sex hormones:

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

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

Substances decreasing the clearance of sex hormones (enzyme inhibitors):

Strong and moderate CYP3A4 inhibitors, such as azole antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem, and grapefruit juice can increase plasma concentrations of the estrogen or dienogest, or both.

Effect of HRT with oestrogens on other medicinal products

Hormone contraceptives containing oestrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. Although the potential interaction between hormone replacement therapy and lamotrigine has not been studied, it is expected that a similar interaction exists, which may lead to a reduction in seizure control among women taking both medicinal products together.

Pharmacodynamic interactions

During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Additionally, also with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs.

Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the following combination drug regimens ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.4).

Other forms of interaction

Laboratory tests

The use of sex steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism, and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range. For more information see section 4.4, “Other conditions”.

4.6 Fertility, pregnancy and lactation

Pregnancy

<invented name> is not indicated during pregnancy. If pregnancy occurs during medication with **<invented name>**, treatment should be withdrawn immediately.

For dienogest no clinical data on exposed pregnancies are available. Studies in animals have not shown reproductive toxicity which could be related to the progest**o**~~a~~genic effects of dienogest (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 estrogens with other progestogens indicate no teratogenic or foetotoxic effect.

Beastfeeding

<invented name> is not indicated during lactation.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. No effects on ability to drive and use machines have been observed in users of <Invented name>.

4.8 Undesirable effects

The following table (System Organ Class MedDRA v. 8.0) attributes frequencies to the undesirable effects of <invented name>. These frequencies are based on the frequencies of adverse events, which were recorded in 4 phase III clinical studies (n = 538 women) and considered as at least possibly related to <inventend name> treatment.

System Organ Class MedDRA v. 8.0	**Common ≥1/100, < 1/10**	**Uncommon ≥1/1,000, < 1/100**
Metabolism and nutrition disorders		Weight increase
Psychiatric disorders		Depression Anorexia nervosa Aggression Somnolence Insomnia Nervousness Anorgasmia Libido decreased
Nervous system disorders	Headache	Migraine Dizziness Paresthesia Hyperkinesia
Vascular disorders		Venous thrombosis (Leg pain) Thrombophlebitis Hypertension Epistaxis
Gastrointestinal disorders	Nausea	Abdominal pain Diarrhea Vomiting Constipation Flatulence Dry mouth
Hepatobiliary disorders		Biliary pain
Skin and subcutaneous tissue disorders		Psoriasis Acne Pruritus Sweating increased Dry skin
Musculoskeletal and connective tissue disorders		Myalgia Cramps legs
Reproductive system and breast disorders	Uterine / Vaginal bleeding including Spotting (bleeding irregularities usually subside during continued treatment) Breast pain Hot flushes	Endometrial disorder Vaginal candidiasis Dysmenorrhea Pruritus genital

General disorders and administration site conditions		Generalized edema / Face edema / Edema Fatigue

Breast cancer risk

An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestagen therapy for more than 5 years.

The increased risk in users of oestrogen-only therapy is lower than that seen in users of oestrogen progestagen combinations.

The level of risk is dependent on the duration of use (see section 4.4).

Absolute risk estimations based on results of the largest randomized placebo-controlled trial (WHI-study) and the largest meta-analysis of prospective epidemiological studies are presented.

Largest meta-analysis of prospective epidemiological studies–Estimated additional risk of breast cancer after 5 years'use in women with BMI 27 (kg/m2)

Age at start HRT (years)	Incidence per 1000 never-users of HRT over a 5 years period (50-54 years)*	Risk ratio	Additional cases per 1000 HRT users after 5 years
Oestrogen only HRT			
50	13.3	1.2	2.7
Combined oestrogen-progestaaogen			
50	13.3	1.6	8.0
* Taken from baseline incidence rates in **England in 2015 in women with BMI 27 (kg/m^2)** Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.			

Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m^2)

Age at start HRT (years)	**Incidence per 1000 never-users of HRT over a 10 years period (50-59 years)***	**Risk ratio**	**Additional cases per 1000 HRT users after 10 years**
Oestrogen only HRT			
50	26.6	1.3	7.1
Combined oestrogen-progestagen			
50	26.6	1.8	20.8
* Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2) Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.			

US WHI studies – additional risk of breast cancer after 5 years'use

Age range (years)	Incidence per 1000	Risk ratio & 95% CI	Additional cases per

	women in placebo arm over 5 years		1000 HRT users over 5 years (95% CI)
CEE oestrogen only			
50-79	21	0.8 (0.7-1.0)	-4 (-6-0) *
CEE+MPA oestrogen & progestagen[1]			
50-79	14~~7~~	1.2 (1.0-1.5)	+4 (0-9)

CEE: conjugated equine estrogen~~s~~. MPA: medroxiprogesterone acetate

* WHI study in women with no uterus, which did not show an increase in risk of breast cancer

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

Endometrial cancer risk

Postmenopausal women with a uterus

The endometrial cancer risk is about 5 in every 1000 women with an uterus not using HRT.

In women with a uterus, use of eoestrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4).

Depending on the duration of oestrogen-only use and oestrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1000 women between the ages of 50 and 65.

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

Ovarian cancer

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

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

Risk of venous thromboembolism

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

WHI Studies- Additional risk of VTE over 5 years'use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users (95% CI)
Oral oestrogen only *			
50-59	7	1.2 (0.6-2.4)	1 (-3 - 10)
Oral combined oestrogen-progestagen			
50-59	4	2.3 (1.2 – 4.3)	5 (1 – 13)
* Study in women with no uterus			

Risk of coronary artery disease

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

Risk of ischaemic stroke

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

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

WHI Studies combined - Additional risk of ischaemic stroke* over 5 years'use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users (95% CI)
50-59	8	1.3 (1.1-1.6)	3 (1-5)
* no differentiation was made between ischaemic and haemorrhagic stroke			

Other adverse reactions have been reported in association with oestrogen/-progestagen treatment:

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

- In women with hereditary angioedema exogenous oestrogens may induce or exacerbate symptoms of angioedema (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V

4.9 Overdose

Acute toxicity studies indicated that, even in the case of inadvertent intake of a multiple of the therapeutic dose, no acute toxicity risk is to be expected. Overdose may cause nausea and vomiting and withdrawal bleeding may occur in some women. There is no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and estrogens, fixed combinations, ATC code:G03F-A15

Estradiol valerate

The active ingredient, synthetic 17ß-estradiol, is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of estrogen production in menopausal women, and alleviates menopausal symptoms.

Dienogest

The active ingredient is a nortestosterone derivative, with an in vitro affinity for the progesterone receptor 10-30 times less compared to other synthetic progestogens. In vivo data in animals demonstrated a strong progestational activity. Dienogest has no significant androgenic, mineralocorticoid, or glucocorticoid activity in vivo.

As estrogens promote the growth of the endometrium, unopposed estrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestogen greatly reduces the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Clinical trial information

- Relief of menopausal symptoms was achieved during the first few weeks of treatment.
- Amenorrhea was seen in 89 % of the women during months 10-12 of treatment.

Breakthroug-bleeding and/or spotting appeared in 27.1 % of the women during the first three months of treatment and in 11 % during months 10-12 of treatment.

5.2 Pharmacokinetic properties

- Estradiol valerate

Absorption

After oral administration estradiol valerate is completely absorbed. Cleavage to estradiol and valeric acid takes place during absorption by the intestinal mucosa or in the course of the first liver passage. Peak serum estradiol concentrations of 21 pg/ml are reached at about 6 hours after single administration of Estradiol Valerate 1 mg/Dienogest 2 mg.

Distribution

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.

Biotransformation

Cleavage to estradiol and valeric acid gives rise to natural estradiol and its metabolites estrone and estriol. The valeric acid undergoes very fast metabolization. After oral administration some 3-6% of the dose is directly bioavailable as estradiol.

Elimination

The plasma half-life of circulating estradiol is about 90 min. After oral administration, however, the situation differs. Because of the large circulating pool of estrogen sulfates and glucuronides, as well as enterohepatic recirculation, the terminal half-life of estradiol after oral administration represents a composite parameter which is dependent on all of these processes and is in the range of about 13-20 h. Its metabolites are mostly excreted with the urine, only about 10% being excreted with the stool.

Steady-state conditions

Following daily ingestion drug serum levels increase about 2.2 fold reaching steady-state conditions after 4-7 days of treatment. Trough, maximum and average estradiol serum concentrations at steady state are 21 pg/ml, 43 pg/ml and 33 pg/ml, respectively. Pharmacokinetics of estradiol are influenced by SHBG levels.

- Dienogest

Absorption

Orally administered dienogest is rapidly and almost completely absorbed. Peak serum concentrations of 49 ng/ml are reached at about 1.5 hours after single ingestion of Estradiol Valerate 1 mg/Dienogest 2 mg. Bioavailability is about 91 %. The pharmacokinetics of dienogest are dose-proportional within the dose range of 1 – 8 mg.

Distribution

Dienogest is bound to serum albumin and does not bind to sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG). 10 % of the total serum drug concentrations are present as free steroid, 90 % are non-specifically bound to albumin. The apparent volume of distribution (Vd/F) of dienogest is 51 l in postmenopausal women.

Biotransformation

Dienogest is nearly completely metabolised by the known pathways of steroid metabolism (hydroxylation, conjugation), mainly by CYP3A4. The pharmacologically inactive metabolites are excreted rapidly resulting in dienogest as the major fraction in plasma accounting for approximately 50% of circulating dienogest derived compounds. The total clearance following the intravenous administration of 3H-dienogest was calculated as 5.1 l/h.

Elimination

The terminal elimination half-life of DNG is 10.5 hours in postmenopausal women after administration of Estradiol Valerate 1 mg/Dienogest 2 mg. Dienogest is excreted in form of metabolites which are excreted at a urinary to faecal ratio of about 3:1 after oral administration of 0.1 mg/kg. The half-life of urinary metabolites excretion is 14 hours. Following oral administration approximately 86% of the dose administered is eliminated within 6 days, the bulk of this amount excreted within the first 24 h, mostly with the urine.

Steady-state conditions

Following daily ingestion drug serum levels increase about 1.3 fold reaching steady-state conditions after 3-4 days of treatment. The pharmacokinetics of dienogest after repeated administration of Estradiol Valerate 1 mg/Dienogest 2 mg can be predicted from single dose pharmacokinetics. Trough, maximum and

average DNG serum concentrations at steady state are 10 ng/ml, 63 ng/ml and 25 ng/ml, respectively.

Pharmacokinetics of dienogest are not influenced by SHBG levels.

No pharmacokinetic information is available on **<invented name>** in patients with renal or hepatic insufficiency.

5.3 Preclinical safety data

Estradiol valerate

The toxicity profile of estradiol is well known. There are no preclinical data of relevance to the prescriber that are additional to those already included in other sections of the SPC.

Dienogest

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Lactose monohydrate
Maize starch
Pregelatinized maize starch
Povidone K30
Magnesium stearate

Coating:

Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol/PEG 3350
Talc
Iron oxide red (E172)
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions

Store in the original package to protect from light.

6.5 Nature and contents of container

Blister of PVC/PVDC/aluminium.

Supplied in cartons containing 28, 3 x 28, or 6 x 28 coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Laboratorios Léon Farma La Vallina s/n, Polígono Industrial. Navatejera,

Villaquilambre-24193 Léon

8. MARKETING AUTHORISATION NUMBER

RVG 113667

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 26 september 2014

Datum van laatste verlenging: 20 juni 2019

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft de rubrieken 4.4 en 4.5: 13 september 2024.