ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

FYLREVY 14.2 mg film-coated tablets
FYLREVY 18.9 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FYLREVY 14.2 mg film-coated tablets

Each film-coated tablet contains 14.2 mg estetrol (as estetrol monohydrate).

Excipient with known effect
Each film-coated tablet contains 42.9 mg lactose monohydrate.

FYLREVY 18.9 mg film-coated tablets

Each film-coated tablet contains 18.9 mg estetrol (as estetrol monohydrate).

Excipient with known effect
Each film-coated tablet contains 37.9 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

FYLREVY 14.2 mg film-coated tablets

The film-coated tablet is orange, 6 mm diameter, round, biconvex with a drop-shaped debossing on one side.

FYLREVY 18.9 mg film-coated tablets

The film-coated tablet is yellow, 6 mm diameter, round, biconvex with a drop-shaped debossing on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in hysterectomised postmenopausal women

Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in non-hysterectomised postmenopausal women with at least 12 months since last menses.

4.2 Posology and method of administration

FYLREVY is an oestrogen-only product.

Posology

One tablet should be taken orally once daily at about the same time with or without food, if necessary, with a small amount of water.
Continuous administration is recommended.

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.

Women with a uterus
The treatment should be initiated with FYLREVY 14.2 mg. If there is insufficient response in the form of alleviated symptoms, the dose could be increased to FYLREVY 18.9 mg.

A progestogen approved for addition to oestrogen treatment should be added continuously.

Hysterectomised women
The dose should be FYLREVY 18.9 mg.

Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestogen in hysterectomised women.

Starting or changing treatment
In women who are not taking HRT, or in women who switch from an oestrogen only HRT product or from a continuous combined HRT product, treatment may be started on any convenient day. In women changing from a cyclic or sequential HRT regimen, treatment should begin on the day following completion of the prior regimen.

Management of missed tablets
If a tablet has been forgotten, it should be taken as soon as possible. If more than 12 hours have elapsed, treatment should be continued with the next tablet without taking the forgotten tablet.

Missed tablets may increase the likelihood of breakthrough bleeding or spotting in women with a uterus.

Hepatic impairment
Estetrol is contraindicated in women with severe hepatic impairment as long as liver function values have not returned to normal (see section 4.3).
No dose adjustment is required in patients with mild or moderate hepatic impairment (see section 5.2).

Renal impairment
Estetrol is not recommended in women with moderate or severe renal impairment.
No dose adjustment is required in patients with mild renal impairment (see section 5.2).

Paediatric population
There is no relevant use of estetrol in the paediatric population for the indication of HRT for oestrogen deficiency symptoms in postmenopausal women.

Elderly
Estetrol has not been studied for safety and efficacy in women initiating treatment over 65 years of age.
No dose recommendation can be made for this population.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- Known, past or suspected breast cancer;
- Known, past or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer);
- Undiagnosed genital bleeding;
- Untreated endometrial hyperplasia;
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism);
- Known 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);
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal;
- Porphyria.

4.4 Special warnings and precautions for use

The percentage of vaginal bleeding was 66.8% and of disordered proliferative endometrium was 5.4% in the pivotal phase 3 study in non-hysterectomised women with at least 12 months since last menses treated with estetrol 18.9 mg continuously combined with progesterone (P4) 100 mg (see also section 4.8). Higher P4 doses or another progestogen approved for addition to oestrogen treatment may be used, however, safety and tolerability data in combination with estetrol are not available.

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

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

Medical examination/follow-up

Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (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 estetrol, in particular:

- Leiomyoma (uterine fibroids) or endometriosis;
- Risk factors for thromboembolic disorders (see below);
- Risk factors for oestrogen dependent tumours, e.g. 1st degree heredity for breast cancer;

- Hypertension;
- Liver disorders (e.g. liver adenoma);
- Diabetes mellitus with or without vascular involvement;
- Cholelithiasis;
- Migraine or (severe) headache;
- Systemic lupus erythematosus;
- A history of endometrial hyperplasia (see below);
- Epilepsy;
- Asthma;
- Otosclerosis.

Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contra-indication is discovered and in the following situations:

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

Endometrial hyperplasia and carcinoma

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

The addition of a progestogen in continuous combined oestrogen-progestagen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.

Break-through bleeding and spotting may occur during the first months of treatment. If break-through 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.

Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestagens to oestrogen replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis, if they are known to have residual endometriosis**.**

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.

Oestrogen-only therapy
The Women's Health Initiative (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 substantially 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 oestrogen-progestagen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Ovarian cancer

Ovarian cancer is much rarer than breast cancer.

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

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

Venous thromboembolism

HRT is associated with a 1.3-3-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 immobilisation, obesity (body mass index (BMI) ≥ 30 kg/m^2), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE.

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

In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening). If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g. antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated.

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

If VTE develops after initiating HRT, the medicinal product should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease (CAD)

There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestagen or oestrogen-only HRT.

Oestrogen-only

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

Ischaemic stroke

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

Other conditions

Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.

Women with pre-existing hypertriglyceridaemia 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.

Exogenous oestrogens 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), thyroxine (T4) levels (by column or by radio-immunoassay) or triiodothyronine (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.

Alanine aminotransferase (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 combined hormonal contraceptives (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.

Excipients

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on estetrol

Estetrol is predominantly glucuronised by UDP-glucuronosyltransferase (UGT) 2B7 enzyme. No clinically relevant interaction was observed with estetrol and the strong UGT inhibitor valproic acid. Cytochrome P450 (CYP450) enzymes do not play a major role in the metabolism of estetrol. An interaction of estetrol with substances known to induce or inhibit CYP450 enzymes is therefore unlikely.

Effects of estetrol on other medicinal products

Based on *in vitro* inhibition studies, an interaction of estetrol with the metabolism of other active substances is unlikely.

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 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).

4.6 Fertility, pregnancy and lactation

Pregnancy

FYLREVY is not indicated during pregnancy. If pregnancy occurs during treatment, it should be withdrawn immediately.

Studies in animals have shown reproductive toxicity (see section 5.3). Based on animal experience, harmful effects due to hormonal action of the active substance cannot be excluded.

The results of most epidemiological studies to date relevant to inadvertent foetal exposure to oestrogens indicate no teratogenic or foetotoxic effects.

Breast-feeding

FYLREVY is not indicated during lactation.

Fertility

FYLREVY is not indicated in women of child-bearing potential.

4.7 Effects on ability to drive and use machines

FYLREVY has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse drug reactions reported in non-hysterectomised postmenopausal women with at least 12 months since last menses exposed to estetrol together with progesterone included endometrial thickening (> 4 mm, 71.3%), vaginal haemorrhage (66.8%) and disordered proliferative endometrium (DPE) (5.4%). The other most frequent adverse drug reactions reported in women with or without a uterus were breast tenderness (8.7%) and breast pain (5.6%). Apart from uterus-related adverse drug reactions, there was no other difference in the safety profile in women with or without a uterus.

Tabulated list of adverse drug reactions
The safety of estetrol was assessed in one phase 2 and two phase 3 clinical trials (Trial 1 and Trial 2) that included 2 606 postmenopausal women (1 290 were treated with estetrol 14.2 mg or 18.9 mg alone, 463 were treated with placebo and 853 with at least 12 months since last menses were treated with estetrol 18.9 mg continuously combined with P4 100 mg).

Adverse drug reactions observed during clinical trials are listed in Table 1 and classified according to frequency and system organ class. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000) very rare (< 1/10 000) and not known (cannot be estimated from the available data).

Table 1: Adverse drug reactions

System organ class	Very common	Common	Uncommon
Infections and infestations		Vulvovaginal candidiasis	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Uterine leiomyoma	
Nervous system disorders		Dizziness	
Vascular disorders			Venous thromboembolism
Gastrointestinal disorders		Abdominal pain lower[a], Abdominal pain, Abdominal distension, Nausea, Constipation	
Skin and subcutaneous tissue disorders			Urticaria
Musculoskeletal and connective tissue disorders		Pain in extremity	
Reproductive system and breast disorders	Vaginal haemorrhage[b], Endometrial thickening	Disordered proliferative endometrium, Breast pain, Breast tenderness, Nipple pain, Uterine spasm,	Endometrial hyperplasia, Endometrial polyp[c], Adenomyosis, Breast mass[d], Breast swelling[e], Ovarian cyst

		Vaginal discharge, Vulvovaginal pruritus	
General disorders and administration site conditions		Asthenia	Peripheral swelling
Investigations		Weight increased	

[a] Includes pelvic pain
[b] Includes uterine haemorrhage and intermenstrual bleeding
[c] Includes cervical polyp and uterine polyp
[d] Includes Phyllodes tumour, breast cyst, breast scan abnormal
[e] Includes breast enlargement, breast engorgement

Description of selected adverse reactions

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 randomised 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/m^2)

Age at start HRT (years)	Incidence per 1 000 never-users of HRT over a 5-year period (50-54 years)*	Risk ratio	Additional cases per 1 000 HRT users after 5 years
Oestrogen-only HRT			
50	13.3	1.2	2.7
Combined oestrogen-progestagen			
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 1 000 never-users of HRT over a 10-year period (50-59 years)*	Risk ratio	Additional cases per 1 000 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 1 000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1 000 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‡			
50-79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)

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

‡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 1 000 women with a uterus not using HRT.

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

Depending on the duration of oestrogen-only use and oestrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1 000 women between the ages of 50 and 65.

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

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

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2 000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2 000 will be diagnosed with ovarian cancer over a 5-year period.

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

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

Age range (years)	Incidence per 1 000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1 000 HRT users
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-progestagen HRT over the age of 60 (see section 4.4).

Risk of ischaemic stroke

- The use of oestrogen-only and oestrogen + progestagen therapy is associated with an up to 1.5-fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.
- This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age, see section 4.4.

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

Age range (years)	Incidence per 1 000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1 000 HRT users over 5 years
50-59	8	1.3 (1.1 – 1.6)	3 (1 – 5)

*no differentiation was made between ischaemic and haemorrhagic stroke.

Reporting of suspected adverse reactions

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

4.9 Overdose

Symptoms of overdose of oestrogen-containing products may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue, and withdrawal bleeding may occur. Based upon studies conducted with single dose of 94.4 mg and multiple doses of 37.8 mg estetrol, symptoms of nipple tenderness and pelvic pain can also occur.
There is no specific antidote, and treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, natural and semisynthetic oestrogens, plain, ATC code: G03CA10

Mechanism of action

The active ingredient, synthetic estetrol, is chemically and biologically identical to endogenous estetrol that is produced during pregnancy by the human foetal liver.

Estetrol substitutes for the loss of oestrogen production in menopausal women, and alleviates menopausal symptoms, including vasomotor symptoms (VMS.

Clinical trial information

The clinical efficacy and safety of estetrol 14.2 mg and estetrol 18.9 mg were assessed in two multicentre phase 3 clinical trials (Trial 1 and Trial 2). Both trials had two parts: Part 1 (randomised, double-blind, placebo-controlled) mainly focused on efficacy and Part 2 (open-label, single arm) on safety.

Relief of oestrogen-deficiency symptoms

The efficacy of estetrol for the relief of VMS was evaluated in postmenopausal women with moderate to severe VMS in Part 1 of Trials 1 and 2. In total, 628 hysterectomised (of whom 419 were treated with estetrol 14.2 mg or 18.9 mg and 209 were treated with placebo) and 591 non-hysterectomised (of whom 392 were treated with estetrol 14.2 mg or 18.9 mg and 199 were treated with placebo) were randomised.

The four co-primary efficacy endpoints for both trials were the change from baseline in the weekly frequency and mean severity of moderate to severe VMS at 4 weeks and 12 weeks.

Relief of menopausal symptoms was achieved during the first few weeks of treatment and maintained throughout the treatment period.

In both pivotal clinical trials, including non-hysterectomised women with at least 12 months since last menses and hysterectomised women, once daily oral doses of estetrol 14.2 mg and estetrol 18.9 mg showed statistically significant reduction in the weekly frequency of moderate to severe VMS at 4 weeks compared to placebo. The statistically significant reduction was maintained at 12 weeks of treatment.

Once daily oral doses of estetrol 18.9 mg showed statistically significant reduction in the severity of moderate to severe VMS at 4 weeks and 12 weeks compared to placebo. A statistically significant reduction in VMS severity was also observed with estetrol 14.2 mg at both time points in Trial 1 but not in Trial 2.

Results (post-hoc analyses) of the change in weekly frequency and mean severity of moderate to severe VMS from Trial 1 Part 1 and Trial 2 Part 1 are presented in Table 2 for estetrol 14.2 mg and Table 3 for estetrol 18.9 mg.

Table 2: Effect of estetrol 14.2 mg on the weekly frequency and mean severity of moderate to severe VMS at week 4 and week 12 – Non-hysterectomised women with at least 12 months since last menses and hysterectomised women (Trial 1, Part 1 and Trial 2, Part 1)

Parameter	Trial 1, Part 1		Trial 2, Part 1	
	Estetrol 14.2 mg	Placebo	Estetrol 14.2 mg	Placebo
	N=200	N=200	N=185	N=185
Frequency of VMS				
Baseline				
Mean (SD)	78.54 (37.832)	76.87 (35.327)	80.32 (51.991)	79.67 (41.013)
Change from baseline to week 4				
LS Mean (SE)	-43.31 (2.984)	-32.17 (3.103)	-42.09 (2.736)	-32.38 (2.801)
LS Mean Difference vs. placebo (SE)	-11.14 (4.299)	-	-9.71 (3.916)	-
95% CI	(-20.64, -1.65)	-	(-18.36, -1.05)	-
p-value vs. placebo	0.0181	-	0.0249	-
Change from baseline to week 12				
LS Mean (SE)	-59.33 (3.098)	-41.81 (3.238)	-58.34 (2.806)	-45.01 (2.916)
LS Mean Difference vs. placebo (SE)	-17.52 (4.475)	-	-13.32 (4.047)	-
95% CI	(-27.41, -7.64)	-	(-22.26, -4.38)	-
p-value vs. placebo	0.0002	-	0.0020	-
Severity of VMS				
Baseline				
Mean (SD)	2.43 (0.280)	2.38 (0.270)	2.46 (0.284)	2.47 (0.236)
Change from baseline to week 4				
LS Mean (SE)	-0.65 (0.071)	-0.37 (0.073)	-0.42 (0.063)	-0.35 (0.065)
LS Mean Difference vs. placebo (SE)	-0.29 (0.102)	-	-0.08 (0.091)	-
95% CI	(-0.51, -0.06)	-	(-0.28, 0.12)	-
p-value vs. placebo	0.0096	-	0.5901	-
Change from baseline to week 12				
LS Mean (SE)	-1.25 (0.074)	-0.71 (0.077)	-0.73 (0.066)	-0.69 (0.068)
LS Mean Difference vs. placebo (SE)	-0.54 (0.107)	-	-0.04 (0.095)	-
95% CI	(-0.78, -0.30)	-	(-0.25, 0.17)	-
p-value vs. placebo	<0.0001	-	0.8533	-

CI: confidence interval; LS Mean: least square mean change from baseline estimated from an MMRM model; MMRM: Mixed-effects Model for Repeated Measures; SD: standard deviation; SE: standard error

Table 3: Effect of estetrol 18.9 mg on the weekly frequency and mean severity of moderate to severe VMS at week 4 and week 12 – Non-hysterectomised women with at least 12 months since last menses and hysterectomised women (Trial 1, Part 1 and Trial 2, Part 1)

Parameter	Trial 1, Part 1		Trial 2, Part 1	
	Estetrol 18.9 mg	Placebo	Estetrol 18.9 mg	Placebo
	N=197	N=200	N=186	N=185
Frequency of VMS				
Baseline				
Mean (SD)	82.32 (50.093)	76.87 (35.327)	79.69 (50.816)	79.67 (41.013)
Change from baseline to week 4				
LS Mean (SE)	-48.45 (2.852)	-32.17 (3.103)	-42.83 (2.699)	-32.38 (2.801)

LS Mean Difference vs. placebo (SE)	-16.28 (4.219)	-	-10.44 (3.889)	-
95% CI	(-25.60, -6.96)	-	(-19.04, -1.85)	-
p-value vs. placebo	0.0002	-	0.0138	-
Change from baseline to week 12				
LS Mean (SE)	-64.46 (2.984)	-41.81 (3.238)	-60.61 (2.789)	-45.01 (2.916)
LS Mean Difference vs. placebo (SE)	-22.65 (4.408)	-	-15.59 (4.035)	-
95% CI	(-32.39, -12.92)	-	(-24.51, -6.67)	-
p-value vs. placebo	<0.0001	-	0.0002	-
Severity of VMS				
Baseline				
Mean (SD)	2.40 (0.273)	2.38 (0.270)	2.47 (0.223)	2.47 (0.236)
Change from baseline to week 4				
LS Mean (SE)	-0.69 (0.068)	-0.37 (0.073)	-0.61 (0.063)	-0.35 (0.065)
LS Mean Difference vs. placebo (SE)	-0.33 (0.100)	-	-0.26 (0.090)	-
95% CI	(-0.55, -0.10)	-	(-0.46, -0.06)	-
p-value vs. placebo	0.0022	-	0.0075	-
Change from baseline to week 12				
LS Mean (SE)	-1.36 (0.072)	-0.71 (0.077)	-1.12 (0.066)	-0.69 (0.068)
LS Mean Difference vs. placebo (SE)	-0.65 (0.106)	-	-0.43 (0.095)	-
95% CI	(-0.89, -0.42)	-	(-0.64, -0.22)	-
p-value vs. placebo	<0.0001	-	<0.0001	-

CI: confidence interval; LS Mean: least square mean change from baseline estimated from an MMRM model; MMRM: Mixed-effects Model for Repeated Measures; SD: standard deviation; SE: standard error

Endometrial safety
The endometrial safety of estetrol 18.9 mg, continuously combined with P4 100 mg was evaluated in 346 non-hysterectomised postmenopausal women in a 1-year open-label trial (Trial 1 Part 2), of whom 325 had an evaluable endometrial biopsy after 1 year. In the sub-population of women with at least 12 months since last menses, endometrial safety was evaluated in 316 women, of which 298 had an evaluable endometrial biopsy after 1 year.

During the clinical trial, assessments of endometrial biopsies taken at 12 months or at early trial discontinuation revealed 1 case of endometrial hyperplasia without atypia, no case of endometrial hyperplasia with atypia and no endometrial cancer (N=1/325, 0.3%; 2-sided 95% CI: 0.0 - 1.7%). In the post-hoc analysis of the sub-population of non-hysterectomised women with at least 12 months since last menses (n=298), the point estimate was 0.3% (2-sided 95% CI: 0.0 - 1.9%).

Bleeding patterns
In Trial 1 Part 2, 853 non-hysterectomised women with at least 12 months since last menses received estetrol 18.9 mg with P4 100 mg continuously for up to 53 weeks. Absence of bleeding or spotting was seen in 37.8% of the women during months 10-12 treatment. Bleeding and/or spotting appeared in 77.2% of the women during the first three months of treatment and in 62.2% during months 10-12 of treatment.

5.2 Pharmacokinetic properties

Absorption

Estetrol is rapidly absorbed after ingestion. After intake of estetrol at doses of 14.2 mg and 18.9 mg in tablet formulation, average peak plasma concentrations of 17.9 ng/mL and 17.3-20.75 ng/mL, respectively, are reached 0.47-0.63 hours after single ingestion. The extent of exposure to estetrol is similar irrespective of food intake. The maximum observed plasma concentration (C_{max}) of estetrol is reduced by approximately 50% after food intake. The peak concentration of estetrol is reached sooner in fasted conditions than in fed conditions (median time of maximum observed plasma concentration (T_{max}) 0.5 hours under fasted conditions compared to 1 hour under fed conditions).

Based on results of the mass balance study the bioavailability of estetrol was estimated at least 69%.

After multiple doses of estetrol 14.2 mg taken once daily for 14 days, the median $T_{max,ss}$ is approximately 0.5 hour. Steady state is achieved after 6 to 8 days. At steady state, the C_{max}, the average concentration and the minimal concentration (trough level) are 16.69 ng/mL, 3.08 ng/mL and 1.42 ng/mL, respectively.

After multiple doses of estetrol 18.9 mg taken once daily for 8 days, the median $T_{max,ss}$ is approximately 0.5 hour. Steady state is achieved after 6 to 8 days. At steady state, the C_{max}, the average concentration and the minimal concentration (trough level) are 19.6 ng/mL, 3.50 ng/mL and 1.59 ng/mL, respectively.

Distribution

The pharmacokinetics of estetrol are characterized by a rapid distribution phase; it is distributed and probably reabsorbed by enterohepatic cycling during the first 18 hours after oral intake. The volume of distribution determined after oral administration of a single dose of 14.2 mg was high indicating that estetrol is widely distributed in tissues.

Estetrol does not bind to SHBG. Estetrol displayed moderate binding to human plasma proteins (45.5 to 50.4%). Estetrol is equally distributed between red blood cells and plasma.

In vitro studies indicated that estetrol is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters. Co-administration of drugs that affect the activity of P-gp and BCRP is however unlikely to result in a clinically relevant drug interaction with estetrol.

Biotransformation

After oral administration, estetrol undergoes extensive phase 2 metabolism to form glucuronide and sulphate conjugates. The two main metabolites estetrol-3-glucuronide and estetrol-16-glucuronide have negligible oestrogenic activity. UGT2B7 is the dominant UGT isoform involved in the biotransformation of estetrol into a direct glucuronide. Estetrol undergoes sulfation, mainly by specific oestrogen sulfotransferase (SULT1E1).

Elimination

The terminal elimination half-life ($t_{1/2}$) of estetrol was observed to be around 24 hours both after single administration and under steady state conditions.

Following administration of a single oral solution of 15 mg [^{14}C]-estetrol, approximately 69% of the total recovered radioactivity was detected in urine and 21.9% in faeces.

Linearity/non-linearity

Estetrol plasma levels do not show any relevant deviation from dose-proportionality over a dose range of 4.7 mg up to 94.4 mg (single administration).

Steady-state conditions

Steady-state is achieved after 6 to 8 days. After once daily repeated oral administration of estetrol 14.2 mg or 18.9 mg, the maximum plasma concentrations of estetrol are about 16.69 ng/mL and 19.60 ng/m, respectively, and are reached 0.18-2 hours after dosing. Average plasma concentrations are 3.08 ng/mL and 3.50 ng/mL, respectively. The accumulation is very limited with daily area under the curve (AUC) at steady-state 60% larger than after a single dose and no observed increase in C_{max}.

Special populations

Hepatic impairment
A study has been performed with a single oral dose of estetrol 18.9 mg administered in female subjects with normal hepatic function, mild hepatic impairment (Child-Pugh class A), moderate hepatic impairment (Child-Pugh class B), and severe hepatic impairment (Child-Pugh class C).

The results show that C_{max} and area AUC_{inf} ratios for estetrol were ~1.7-fold and ~1.1-fold, respectively, in mild hepatic impairment versus subjects with normal hepatic function, ~1.9-fold and ~1-fold, respectively, in moderate hepatic impairment versus subjects with normal hepatic function, and ~5.4-fold and ~1.9-fold, respectively, in severe hepatic impairment versus subjects with normal hepatic function (see section 4.2).

Renal impairment
A study to evaluate the effect of renal disease on pharmacokinetics of estetrol was performed with a single oral dose of estetrol 18.9 mg administered in female subjects with normal renal function, mild renal impairment (absolute glomerular filtration rate (GFR < 90 to ≥ 60 mL/min), moderate renal impairment (GFR < 60 to ≥ 30 mL/min) and severe renal impairment (GFR < 30 mL/min).

C_{max} and AUC_{inf} for estetrol were ~1.1-fold and ~1.7-fold, respectively, in mild renal impairment versus subjects with normal renal function; ~1.8-fold and ~2.3-fold, respectively, in moderate renal impairment versus subjects with normal renal function, and ~1.5-fold and ~2.3-fold, respectively, in severe renal impairment versus subjects with normal renal function.

Renal clearance (CLr) was decreased by 20% in the group with mild renal impairment, 40% in the group with moderate renal impairment, and 71% in the group with severe renal impairment compared to the group with normal renal function.

The study results indicate that the increase of estetrol plasma exposure in subjects with moderate and severe renal impairment compared to subjects with a normal renal function could be of clinical relevance (see section 4.2).

Other special populations

Ethnic groups
No clinically relevant differences in the pharmacokinetics of estetrol between Japanese and Caucasian women have been observed after single dose administration of estetrol 14.2 mg.

5.3 Preclinical safety data

Repeated dose toxicity studies with estetrol have indicated expected oestrogenic effects.
In particular, reproduction toxicity studies revealed embryonic and foetotoxic effects in animals which are considered as species specific.

Estetrol is not considered to be genotoxic. However, it is known that due to their hormonal action, sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

Environmental risk assessment studies have shown that estetrol may pose a risk to the aquatic environment and to the groundwater compartment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Sodium starch glycolate (Type A)
Maize starch
Povidone K30
Magnesium stearate (E572)

Tablet coating
Hypromellose (E464)
Hydroxypropylcellulose (E463)
Talc (E553b)
Cottonseed oil, hydrogenated
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (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 storage conditions.

6.5 Nature and contents of container

Transparent PVC/aluminium blister containing 28 film-coated tablets in a carton with an etui storage case.

Pack sizes

28, 84 or 168 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3).

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

7. MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

8. MARKETING AUTHORISATION NUMBER(S)

FYLREVY 14.2 mg film-coated tablets
EU/1/26/2020/001
EU/1/26/2020/002
EU/1/26/2020/003

FYLREVY 18.9 mg film-coated tablets
EU/1/26/2020/004
EU/1/26/2020/005
EU/1/26/2020/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Gedeon Richter Plc.
Gyömrői út 19-21
1103 Budapest
Hungary

Haupt Pharma Münster GmbH
Schleebrüggenkamp 15
48159 Münster
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this medicinal product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

FYLREVY 14.2 mg film-coated tablets
estetrol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 14.2 mg estetrol (as estetrol monohydrate).

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

28 film-coated tablets
84 film-coated tablets
168 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2020/001
EU/1/26/2020/002
EU/1/26/2020/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

FYLREVY 14.2 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

FYLREVY 14.2 mg film-coated tablets
estetrol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON ETUI STORAGE CASE **ETUI STORAGE CASE**

Fylrevy

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

FYLREVY 18.9 mg film-coated tablets
estetrol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 18.9 mg estetrol (as estetrol monohydrate).

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

28 film-coated tablets
84 film-coated tablets
168 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2020/004
EU/1/26/2020/005
EU/1/26/2020/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

FYLREVY 18.9 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

FYLREVY 18.9 mg film-coated tablets
estetrol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON ETUI STORAGE CASE **ETUI STORAGE CASE**

Fylrevy

B. PACKAGE LEAFLET

Package leaflet: Information for the user

FYLREVY 14.2 mg film-coated tablets
FYLREVY 18.9 mg film-coated tablets
estetrol

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What FYLREVY is and what it is used for

FYLREVY is a hormone replacement therapy (HRT). It contains the natural oestrogen hormone, estetrol. FYLREVY is used in:
- postmenopausal women who have had their uterus (womb) removed (have had a hysterectomy), and;
- postmenopausal women with an intact uterus (have not had a hysterectomy) and who have not had a natural menstrual period for at least 12 months.

Relief of symptoms occurring after menopause
During the menopause, the amount of the oestrogen produced by a woman's body drops. This can cause symptoms such as hot face, neck and chest ("hot flushes"). FYLREVY alleviates these symptoms after menopause. You will only be prescribed FYLREVY if your symptoms seriously hinder your daily life.

2. What you need to know before you take FYLREVY

Medical history and regular check-ups
The use of HRT carries risks which need to be considered when deciding whether to start taking it, or whether to carry on taking it.

The experience in treating women with a premature menopause (due to ovarian failure or surgery) is limited. If you have a premature menopause the risks of using HRT may be different. Please talk to your doctor.

Before you start (or restart) HRT, your doctor will ask about your own and your family's medical history. Your doctor may decide to perform a physical examination. This may include an examination of your breasts and/or an internal examination, if necessary.

Once you have started on FYLREVY you should see your doctor for regular check-ups (at least once a year). At these check-ups, discuss with your doctor the benefits and risks of continuing with FYLREVY.

Go for regular breast screening, as recommended by your doctor.

Do not take FYLREVY
If any of the following applies to you. If you are not sure about any of the points below, **talk to your doctor** before taking FYLREVY.

Do not take FYLREVY:
- If you are **allergic** (hypersensitive) to **estetrol**, or any of the other ingredients of this medicine (listed in section 6);
- If you have or have ever had **breast cancer**, or if you are suspected of having it;
- If you have **cancer which is sensitive to oestrogens**, such as cancer of the womb lining (endometrium), or if you are suspected of having it;
- If you have any **unexplained vaginal bleeding**;
- If you have **excessive thickening of the womb lining** that is not being treated;
- If you have or have ever had a **blood clot in a vein** (thrombosis), such as in the legs (deep venous thrombosis) or the lungs (pulmonary embolism);
- If you have a **blood clotting disorder** (such as protein C, protein S, or antithrombin deficiency);
- If you have or recently have had a disease caused by blood clots in the arteries, such as a **heart attack, stroke or angina**;
- If you have or have ever had a **liver disease** and your liver function tests have not returned to normal;
- If you have a rare blood problem called "porphyria" which is passed down in families (inherited).

If any of the above conditions appear for the first time while taking FYLREVY, stop taking it at once and consult your doctor immediately.

Warnings and precautions
Talk to your doctor or pharmacist before taking FYLREVY.

Tell your doctor if you have ever had any of the following problems, before you start the treatment, as these may return or become worse during treatment with FYLREVY. If so, you should see your doctor more often for check-ups:
- fibroids inside your womb;
- growth of womb lining outside your womb (endometriosis) or a history of excessive growth of the womb lining (endometrial hyperplasia);
- increased risk of developing blood clots (see "Blood clots in a vein (thrombosis)");
- increased risk of getting an oestrogen-sensitive cancer (such as having a mother, sister or grandmother who has had breast cancer);
- high blood pressure;
- a liver disorder, such as a benign liver tumour;
- diabetes;
- gallstones;
- migraine or severe headaches;
- a disease of the immune system that affects many organs of the body (systemic lupus erythematosus, SLE);
- epilepsy;
- asthma;

- a disease affecting the eardrum and hearing (otosclerosis);
- a very high level of fat in your blood (triglycerides);
- fluid retention due to cardiac or kidney problems;
- hereditary and acquired angioedema.

Stop taking FYLREVY and see a doctor immediately
If you notice any of the following when taking HRT:
- any of the conditions mentioned in the 'DO NOT take FYLREVY' section;
- yellowing of your skin or the whites of your eyes (jaundice). These may be signs of a liver disease;
- swollen face, tongue and/or throat and/or difficulty swallowing or hives, together with difficulty breathing which are suggestive of an angioedema;
- a large rise in your blood pressure (symptoms may be headache, tiredness, dizziness);
- migraine-like headaches which happen for the first time;
- if you become pregnant;
- if you notice signs of a blood clot, such as:
  - painful swelling and redness of the legs;
  - sudden chest pain;
  - difficulty in breathing;

  For more information, see 'Blood clots in a vein (thrombosis)'

Note: FYLREVY is not a contraceptive. If it is less than 12 months since your last menstrual period or you are under 50 years old, you may still need to use additional contraception to prevent pregnancy. Speak to your doctor for advice.

HRT and cancer

Excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the lining of the womb (endometrial cancer)

Taking oestrogen-only HRT will increase the risk of excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the womb lining (endometrial cancer).

Taking a progestogen in addition to the oestrogen for at least 12 days of each 28-day cycle protects you from this extra risk. So, your doctor will prescribe a progestogen separately if you still have your womb. If you have had your womb removed (a hysterectomy), discuss with your doctor whether you can safely take this product without a progestogen.

In women who still have a womb and who are not taking HRT, on average, 5 in 1 000 will be diagnosed with endometrial cancer between the ages of 50 and 65.

For women aged 50 to 65 who still have a womb and who take oestrogen-only HRT, between 10 and 60 women in 1 000 will be diagnosed with endometrial cancer (i.e. between 5 and 55 extra cases), depending on the dose and for how long it is taken.

FYLREVY contains a higher dose of oestrogens than other oestrogen-only HRT products. The risk of endometrium cancer when using together with a progestogen is not known.

Breast cancer
Evidence shows that taking combined oestrogen-progestogen and or oestrogen-only HRT increases the risk of breast cancer. The extra risk depends on how long you use HRT. The additional risk becomes clear within 3 years of use. After stopping HRT, the extra risk will decrease with time, but the risk may persist for 10 years or more if you have used HRT for more than 5 years.

Compare
Women aged 50 to 54 who are not taking HRT, on average, 13 to 17 in 1 000 will be diagnosed with breast cancer over a 5-year period.

For women aged 50 who start taking oestrogen-only HRT for 5 years, there will be 16-17 cases in 1 000 users (i.e. an extra 0 to 3 cases).

For women aged 50 who start taking oestrogen-progestogen HRT for 5 years, there will be 21 cases in 1 000 users (i.e. an extra 4 to 8 cases).

Women aged 50 to 59 who are not taking HRT, on average, 27 in 1 000 will be diagnosed with breast cancer over a 10-year period.

For women aged 50 who start taking oestrogen-only HRT for 10 years, there will be 34 cases in 1 000 users (i.e. an extra 7 cases).

For women aged 50 who start taking oestrogen-progestogen HRT for 10 years, there will be 48 cases in 1 000 users (i.e. 21 extra cases).

Regularly check your breasts. See your doctor if you notice any changes such as:
- dimpling of the skin;
- changes in the nipple;
- any lumps you can see or feel;

Additionally, you are advised to join mammography screening programs when offered to you. For mammogram screening, it is important that you inform the nurse/healthcare professional who is actually taking the x-ray that you use HRT, as this medication may increase the density of your breasts which may affect the outcome of the mammogram. Where the density of the breast is increased, mammography may not detect all lumps.

Ovarian cancer
Ovarian cancer is rare - much rarer than breast cancer. The use of oestrogen-only or combined oestrogen-progestogen HRT has been associated with a slightly increased risk of ovarian cancer.

The risk of ovarian cancer varies with age. For example, in women aged 50 to 54 who are not taking HRT, about 2 women in 2 000 will be diagnosed with ovarian cancer over a 5-year period. For women who have been taking HRT for 5 years, there will be about 3 cases per 2 000 users (i.e. about 1 extra case).

Effect of HRT on heart and circulation

Blood clots in a vein (thrombosis)
The risk of **blood clots in the veins** is about 1.3 to 3 times higher in HRT users than in non-users, especially during the first year of taking it.

Blood clots can be serious, and if one travels to the lungs, it can cause chest pain, breathlessness, fainting or even death.

You are more likely to get a blood clot in your veins as you get older and if any of the following applies to you. Inform your doctor if any of these situations applies to you:
- you are unable to walk for a long time because of major surgery, injury or illness (see also section 3, If you need to have surgery);
- you are seriously overweight (BMI > 30 kg/m^2);
- you have any blood clotting problem that needs long-term treatment with a medicine used to prevent blood clots;
- if any of your close relatives has ever had a blood clot in the leg, lung or another organ;
- you have systemic lupus erythematosus (SLE);
- you have cancer;

For signs of a blood clot, see “Stop taking FYLREVY and see a doctor immediately”.

Compare
Looking at women in their 50s who are not taking HRT, on average, over a 5-year period, 4 to 7 in 1 000 would be expected to get a blood clot in a vein.

For women in their 50s who have been taking oestrogen-progestogen HRT for over 5 years, there will be 9 to 12 cases in 1 000 users (i.e.an extra 5 cases).

For women in their 50s who have had their womb removed and have been taking oestrogen-only HRT for over 5 years, there will be 5 to 8 cases in 1 000 users (i.e. 1 extra case).

Heart disease (heart attack)
There is no evidence that HRT will prevent a heart attack.

Women over the age of 60 years who use oestrogen-progestogen HRT are slightly more likely to develop heart disease than those not taking any HRT.

For women who have had their womb removed and are taking oestrogen-only therapy there is no increased risk of developing heart disease.

Stroke
The risk of getting a stroke is about 1.5 times higher in HRT users than in non-users. The number of extra cases of stroke due to use of HRT will increase with age.

Compare
Looking at women in their 50s who are not taking HRT, on average, 8 in 1 000 would be expected to have a stroke over a 5-year period. For women in their 50s who are taking HRT, there will be 11 cases in 1 000 users, over 5 years (i.e. an extra 3 cases).

Other conditions
- HRT will not prevent memory loss. There is some evidence of a higher risk of memory loss in women who start using HRT after the age of 65. Speak to your doctor for advice.

Children and adolescents
FYLREVY should not be taken by children and adolescents.

Other medicines and FYLREVY
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines including medicines obtained without a prescription, herbal medicines or other natural products.

Some medicines may interfere with the effect of some HRTs. FYLREVY has a low potential for interacting with other drugs.

HRT can affect the way some other medicines work:
- Medicines for Hepatitis C virus (HCV) (such as combination regimens ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin; glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir may cause increases in liver function blood test results (increase in alanine aminotransferase (ALT) liver enzyme) in women using CHCs containing ethinylestradiol. FYLREVY contains estetrol instead of ethinylestradiol. It is not known whether an increase in ALT liver enzyme can occur when using FYLREVY with this HCV combination regimen.

Laboratory tests
If you need a blood test, tell your doctor or the laboratory staff that you are taking FYLREVY, because this medicine can affect the results of some tests.

FYLREVY with food and drink
FYLREVY may be taken with or without food, if necessary, with a small amount of water.

Pregnancy and breast-feeding
FYLREVY is for use in postmenopausal women only. If you become pregnant, stop taking FYLREVY and contact your doctor.

Driving and using machines
FYLREVY has no or negligible influence on the ability to drive and use machines.

FYLREVY contains lactose and sodium
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

3. How to take FYLREVY

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will aim to prescribe the lowest dose to treat your symptom for as short as necessary.
In women without a uterus (womb), FYLREVY 18.9 mg should be used.

Speak to your doctor if you think this dose is too strong or not strong enough.

Take one tablet each day at about the same time, with some water if necessary.
Continuous administration is recommended.

Women with an intact uterus may experience irregular vaginal bleeding or spotting (minimal blood loss requiring at most one tampon) while taking FYLREVY, mainly during the first 3 months of treatment. In case of persistent or significant vaginal bleeding, talk to your doctor.
If you still have a uterus, FYLREVY must be taken in combination with a progestogen continuously as prescribed by your doctor.

If you take more FYLREVY than you should
There are no reports of serious harmful results of taking too many FYLREVY tablets.
If you take several FYLREVY tablets at once, you may feel sick, experience low abdominal pain, nipple pain, or vomit or bleed from the vagina.
If you have taken too many FYLREVY tablets, or you discover that a child has taken some, ask your doctor or pharmacist for advice.

If you forget to take FYLREVY
If you forgot to take a tablet at your usual time, it should be taken as soon as possible. If more than 12 hours have passed, do not take the forgotten tablet and take the next tablet at the usual time. Do not take an extra table to make up for a forgotten dose.

Missed tablets may increase the likelihood of breakthrough bleeding or spotting in women with a uterus.

If you stop taking FYLREVY
You can stop taking FYLREVY at any time. You should talk to your doctor before stopping to take FYLREVY.

If you need to have surgery
If you are going to have surgery, tell the surgeon that you are taking FYLREVY. You may need to stop taking FYLREVY about 4 to 6 weeks before the operation to reduce the risk of a blood clot (see section 2, Blood clots in a vein). Ask your doctor when you can start taking FYLREVY again.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following diseases are reported more often in women using HRT compared to women not using HRT:
- breast cancer;
- abnormal growth or cancer of the lining of the womb (endomethrial hyperplasia or cancer);
- ovarian cancer;
- blood clots in the veins of the legs or lungs (venous thromboembolism);
- heart disease;
- stroke;
- probable memory loss if HRT is started over the age of 65.

There is no experience with estetrol-containing HRT.
For more information about these side effects, see section 2.

The following side effects have been reported while using FYLREVY:

Very common (may affect more than 1 in 10 people):
- vaginal bleeding;
- thickening of the lining of the womb (endometrial thickening);

Common (may affect up to 1 in 10 people):
- vaginal fungal infection (candidiasis);
- non-cancerous growth of the womb (uterine leiomyoma);
- dizziness;
- lower belly (abdominal) pain,
- belly (abdominal) pain;
- bloating;
- feeling sick (nausea);
- constipation
- pain in arms or legs (pain in extremity);
- abnormal growth of the lining of the womb (disordered proliferative endometrium);
- pain in the breasts;
- tender breasts;
- pain in the nipples;
- contractions of the womb;
- vaginal discharge;
- itchy vulva or vagina (vulvovaginal pruritus)
- extreme tiredness (asthenia);
- increase in weight.

Uncommon (may affect up to 1 in 100 people):
- harmful blood clots in a vein for example
  - in a leg or foot (deep vein thrombosis)
  - in a lung (i.e. pulmonary embolism)
- itchy skin rash (urticaria);

- excessive thickening of the lining of the womb (endometrial hyperplasia);
- polyps (small growths) in the womb;
- the lining of the womb (endometrium) growing into the muscle layer of the womb (adenomyosis);
- lump in the breasts;
- swollen breasts;
- sac of fluid within the ovaries (ovarian cyst);
- swelling in arms or legs (peripheral swelling).

The following side effects have been reported with other HRTs:
- gall bladder disease;
- various skin disorders:
  - discoloration of the skin especially of the face or neck known as “pregnancy patches” (chloasma);
  - painful reddish skin nodules (erythema nodosum);
  - rash with target-shaped reddening or sores (erythema multiforme).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store FYLREVY

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What FYLREVY contains
- The active substance is estetrol.

FYLREVY 14.2 mg film-coated tablets
Each film-coated tablet contains 14.2 mg estetrol (as estetrol monohydrate).

FYLREVY 18.9 mg film-coated tablets
Each film-coated tablet contains 18.9 mg estetrol (as estetrol monohydrate).

- The other ingredients are:
  Tablet core: Lactose monohydrate, sodium starch glycolate (see section 2, ‘FYLREVY contains lactose and sodium’), maize starch, povidone K30, magnesium stearate (E572).
  Tablet coating: Hypromellose (E464), hydroxypropylcellulose (E463), talc (E553b), cottonseed oil, hydrogenated, titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172).

What FYLREVY looks like and contents of the pack

FYLREVY 14.2 mg film-coated tablets

The film-coated tablets are orange, 6 mm diameter, round, biconvex with a drop-shaped debossing on one side.

FYLREVY 18.9 mg film-coated tablets
The film-coated tablets are yellow, 6 mm diameter, round, biconvex with a drop-shaped debossing on one side.

FYLREVY is presented in transparent PVC/aluminium blisters of 28 film-coated tablets packed in a carton with an etui storage case.

Pack sizes: 28, 84 or 168 film-coated tablets.

Not all pack sizes may be marketed.

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1103 Budapest
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Manufacturer
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Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.