Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Femurest-conti 1 mg/5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg 17β-estradiol (as hemihydrate) and 5 mg dydrogesterone.

Excipient(s) with known effect: lactose monohydrate 114.7mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated 'tablet'

Round, biconvex tablet marked 379 on one side (7mm)
Salmon coloured 1/5 mg tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women at least 12 months since last menses.
Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.

(See also section 4.4)

The experience in treating women older than 65 years is limited.

4.2 Posology and method of administration

Femurest-conti ® 1 mg/5 mg is a continuous combined HRT for oral use.
The oestrogen and the progstogen are given every day without interruption.

The dosage is one tablet per day for a 28 day cycle.
Femurest-conti ® 1 mg/5 mg should be taken continuously without a break between packs.
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.

Continuous combined treatment may be started with Femurest-conti ® 1 mg/5 mg depending on the time since menopause and severity of symptoms. Women experiencing a natural menopause should commence treatment with Femurest-conti ® 1 mg/5 mg 12 months after their last natural menstrual bleed. For surgically induced menopause, treatment may start immediately.

Depending on the clinical response, the dosage can subsequently be adjusted.

Patients changing from a continuous sequential or cyclical preparation should complete the 28 day cycle and then change to Femurest-conti ® 1 mg/5 mg.
Patients changing from another continuous combined preparation may start therapy at any time.

If a dose 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. The likelihood of breakthrough bleeding or spotting may be increased.

Femurest-conti ® 1 mg/5 mg can be taken irrespectively of food intake.

Paediatric population:
There is no relevant indication for the use of Femurest-conti ® 1 mg/5 mg in the paediatric population.

4.3 Contraindications

- Known, past or suspected breast cancer,
- Known 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),
- Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal,
- Porphyria.
- Known hypersensitivity to the active substances or to any of the excipients listed in section 6.1

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 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 Femurest conti, 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
- Meningioma

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 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-progestogen therapy in non-hysterectomised women can prevent 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.

Breast cancer
The overall evidence suggests an increased risk of breast cancer in women taking combined oestrogen-progestogen and possibly also oestrogen-only HRT, that is dependent on the duration of taking HRT.

Combined oestrogen-progestogen therapy:

- The randomised placebo-controlled trial, the Women's Health Initiative study (WHI) and epidemiological studies are consistant in finding an increased risk of breast cancer in women taking combined oestrogen-progestagen for HRT that becomes apparent after about 3 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 substantially lower than that found in users of oestrogen-progestogen combinations (see section 4.8).

The excess risk becomes apparent within a few years of use and increases with duration of intake but returns to baseline within a few (at most five) years after stopping treatment.

HRT, especially oestrogen-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 the 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 oestrogen, older age, major surgery, prolonged immobilisation, obesity (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 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 (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-progestogen 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

- Oestrogens may cause fluid retention and therefore patients with cardiac or renal dysfunction should be carefully observed.
- Women with pre-existing hypertriglyceridemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition.
- 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 radio-immunoassay) 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-1-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.

- Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- This oestrogen-progestogen combination treatment is not a contraceptive.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

The efficacy of oestrogens and progestogens might be impaired
- The metabolism of estrogens and progestagens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (eg. phenobarbital, carbamazepine, phenytoin) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).
- Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones.
- Herbal preparations containing St John's wort (Hypericum perforatum) may induce the metabolism of estrogens and progestagens.
- Clinically an increased metabolism of estrogens and progestagens may lead to decreased effect and changes in the uterine bleeding profile.

4.6 Fertility, pregnancy and lactation

Pregnancy
Femurest-conti is not indicated during pregnancy. If pregnancy occurs during medication with Femurest-conti, treatment should be withdrawn immediately.

There are no adequate data from the use of estradiol/dydrogesterone in pregnant women. The results of most epidemiological studies to date relevant to inadvertent fetal exposure to combinations of estrogens and progestagens indicate no teratogenic or fetotoxic effect. .

Breast-feeding
Femurest-conti is not indicated during lactation.

Fertility
Femurest-conti is not indicated during fertility

4.7 Effects on ability to drive and use machines

Femurest-conti has no or negligible influence on the ability to drive and/or use machines.

4.8 Undesirable effects

The most commonly reported adverse drug reactions of patients treated with estradiol/ dydrogesterone in clinical trials are headache, abdominal pain, breast pain/tenderness and back pain.

The following undesirable effects have been observed with the frequencies indicated below during clinical trials (N=4929).
*Undesirable effects from spontaneous reporting not observed in clinical trials have been attributed to the frequency "rare".

MedDRA system organ	Very Common ≥1/10	Common >1/100, <1/10	Uncommon >1/1,000, <1/100	Rare >1/10,000,

class				<1/1,000
Infections and infestations		Vaginal candidiasis	Cystitis-like symptoms	
Neoplasms benign, malignant and unspecified			Increase in size of leiomyoma	
Blood and the lymphatic system disorders				Haemolytic anaemia*
Immune system disorders			Hypersensitivity	
Psychiatric disorders		Depression, nervousness	Influence on libido	
Nervous system disorders	Headache	Migraine, dizziness		Meningioma*
Eye disorders				Steepening of corneal curvature*, contact lense intolerance*
Cardiac disorders				Myocardial infarction
Vascular disorders			Venous thromboembolism*, hypertension, peripheral vascular disease, varicose vein,	Stroke*
Gastrointestinal disorders	Abdominal pain	Nausea, vomiting, abdominal distension (including flatulence)	Dyspepsia	
Hepatobiliary disorders			Abnormal hepatic function, occasionally with jaundice, asthenia or malaise and abdominal pain, gall bladder disorders	
Skin and subcutaneous tissue disorders		Allergic skin reactions (e.g. rash, urticarial, pruritus)		Angioedema, vascular purpura, erythema nodosumU*, Chloasma or melasma, which may persist when drug is

				discontinued
Musculoskeletal and connective tissue disorders	Back pain			Leg cramps
Reproductive system and breast disorders	Breast pain /tenderness	Menstrual disorders (including postmenopausal spotting, metrorrhagia, menorrhagia, oligo-/amenorrhoea, irregular menstruation, dysmennorrhoea), pelvic pain, cervical discharge	Breast enlargement, premenstrual-syndrome	
General disorders and administration site reactions		Asthenic conditions (asthenia, fatigue, malaise), peripheral oedema		
Investigations		Increased weight	Decreased weight	

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestogen therapy for more than 5 years.
- Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestogen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- Results of the largest randomised placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

Million Women study– Estimated additional risk of breast cancer after 5 years' use

Age range (years)	Additional cases per 1000 never-users of HRT over a 5 year period[a]	Risk ratio [#]	Additional cases per 1000 HRT users over 5 years (95%CI)
		Oestrogen only HRT	
50 - 65	9 - 12	1.2	1 - 2 (0 - 3)
		Combined oestrogen-progestogen	
50 - 65	9 - 12	1.7	6 (5 - 7)

[#]Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use
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 (yrs)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95% CI	Additional cases per 1000 HRT users over 5 years (95% CI)
		CEE oestrogen-only	
50 - 79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)[b]
		CEE+MPA oestrogen & progestogen[‡]	
50 - 79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)

[‡]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 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 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 the risk of endometrial cancer (RR of 1.0 (0.8 - 1.2)).

Ovarian cancer

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

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

Risk of venous thromboembolism

HRT is associated with a 1.3 to 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 and 95%CI	Additional cases per 1000 HRT users
Oral oestrogen-only[c]			
50 - 59	7	1.2 (0.6 - 2.4)	1 (-3 – 10)
Oral combined oestrogen-progestogen			
50 - 59	4	2.3 (1.2 – 4.3)	5 (1 - 13)

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 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[d] over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users over 5 years
50 - 59	8	1.3 (1.1 - 1.6)	3 (1 - 5)

Other adverse reactions have been reported in association with oestrogen/progestogen treatment

Neoplasms benign, malignant and unspecified:

Oestrogen dependent neoplasms both benign and malignant, e.g. endometrial cancer, ovarian cancer. Increase in size of meningioma.

Immune system disorders:

Systemic lupus erythematosus

Metabolism and nutrition disorders:

Hypertriglyceridemia

Nervous system disorders:

Probable dementia, chorea, exacerbation of epilepsy

Vascular disorders:

Arterial thromboembolism

Gastrointestinal disorders:

Pancreatitis (in women with pre-existing hypertriglyceridemia)

Skin and subcutaneous tissue disorders:

Erythema multiforme

Renal and urinary disorders:

Urinary incontinence

Reproductive system and breast disorders:

Fibrocystic breast disease, uterine cervical erosion

Congenital, familial and genetic disorders:

Aggravated porphyria

Investigations:

Total thyroid hormones increased

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

[a] Taken from baseline incidence rates in developed countries

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

[c] Study in women with no uterus
[d] No differentiation was made between ischaemic and haemorrhagic stroke

4.9 Overdose

Both estradiol and dydrogesterone are substances with low toxicity. Symptoms such as nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness / fatigue and withdrawal bleeding could occur in cases of overdosing. It is unlikely that any specific or symptomatic treatment will be necessary.
Paediatric Population:
Aforementioned information is applicable for overdosing by children also.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Genito urinary system and sex hormones, progestogens and estrogens, fixed combinations.
The ATC code is G03 F A14

Estradiol
The active ingredient, synthetic 17β-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. Estrogens prevent bone loss following menopause or ovariectomy.

Dydrogesterone
Dydrogesterone is an orally-active progestogen having an activity comparable to parenterally administered progesterone.

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

Clinical trial information
- Relief of estrogen-deficiency symptoms and bleeding patterns
- Relief of menopausal symptoms was achieved during the first few weeks of treatment.

  Amenorrhoea (no bleeding or spotting) was seen in 88% of women during months 10 -12 of treatment. Irregular bleeding and/or spotting appeared in 15% of the women during the first three months of treatment and in 12% during months 10 -12 of treatment.

Prevention of osteoporosis
- Oestrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass. The effect of estrogens on the bone mineral density is dose-dependent. Protection appears to be effective for as long as treatment is continued. After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women.

  Evidence from the WHI trial and meta-analysed trials shows that current use of HRT, alone or in combination with a progestagen – given to predominantly healthy women – reduces the risk of hip, vertebral, and other osteoporotic fractures. HRT may also prevent fractures in women with low bone density and/or established osteoporosis, but the evidence for that is limited.

After one year of treatment with Femurest-conti, the increase in lumbar spine bone mineral density (BMD) was 4.0% ± 3.4 % (mean ± SD). The percentage of women who maintained or gained BMD in lumbar zone during treatment was 90%.
Femurest-conti also had an effect on hip BMD. The increase after one year of treatment was 1.5% ± 4.5 % (mean ± SD) at femoral neck, 3.7% +/- 6.0% (mean ± SD) at trochanter and 2.1% ± 7.2% (mean ± SD) at Wards triangle. The percentage of women who maintained or gained BMD in the 3 hip areas during treatment was 71, 66 and 81%

respectively.

5.2 Pharmacokinetic properties

Estradiol

- Absorption:

Absorption of estradiol is dependent on the particle size: micronized estradiol is readily absorbed from the gastrointestinal tract.

The following table provides the mean steady state pharmacokinetic parameters of estradiol (E2), estrone (E1) and estrone sulphate (E1S) for each dose of micronized estradiol. Data is presented as mean (SD):

Estradiol 1mg				
Parameters	E2	E1	Parameters	E1S
Cmax (pg/mL)	71 (36)	310 (99)	Cmax (pg/mL)	9.3 (3.9)
Cmin (pg/mL)	18.6 (9.4)	114 (50)	Cmin (pg/mL)	2.099 (1.340)
Cav (pg/mL)	30.1 (11.0)	194 (72)	Cav (pg/mL)	4.695 (2.350)
AUC_{0-24} (pg.h/mL)	725 (270)	4767 (1857)	AUC_{0-24} (ng.h/mL)	112.7 (55.1)

- Distribution:

Oestrogens can be found either unbound or bound. About 98-99% of the estradiol dose binds to plasma proteins, from which about 30-52% to albumin and about 46-69% to the sex hormone-binding globulin (SHBG)

- Biotransformation:

Following oral administration, estradiol is extensively metabolised. The major unconjugated and conjugated metabolites are estrone and estrone sulphate. These metabolites can contribute to the oestrogen activity, either directly or after conversion to estradiol. Estrone sulphate may undergo enterohepatic circulation.

- Elimination:

In urine, the major compounds are the glucuronides of estrone and estradiol. The elimination half-life is between 10-16 h.
Oestrogens are secreted in the milk of nursing mothers.

- Dose and time dependencies:

Following daily oral administration of Femurest-conti, estradiol concentrations reached a steady-state after about five days.
Generally, steady state concentrations appeared to be reached for within 8 to 11 days of dosing.

Dydrogesterone

- Absorption:

Following oral administration, dydrogesterone is rapidly absorbed with a T_{max} between 0.5 and 2.5 hours. The absolute bioavailability of dydrogesterone (oral 20 mg dose versus 7.8 mg intravenous infusion) is 28%.

The following table provides the mean single dose pharmacokinetic parameters of dydrogesterone (D) and dihydrodydrogesterone (DHD). Data is presented as mean (SD):

Dydrogesterone 5mg		
Parameters	D	DHD
Cmax (ng/mL)	0.980 (0.59)	24.68 (10.89)
AUC_{0-t} (ng.h/mL)	1.55 (1.08)	98.37 (43.21)
AUC_{inf} (ng.h/mL)	-	121.36 (63.63)

- Distribution:

After intravenous administration of dydrogesterone the steady-state volume of distribution is approximately 1400 L. Dydrogesterone and DHD are more than 90% bound to plasma proteins.

- Biotransformation:

Following oral administration, dydrogesterone is rapidly metabolised to DHD. The levels of the main active metabolite 20 α-dihydrodydrogesterone (DHD) peak about 1.5 hours postdose. The plasma levels of DHD are substantially higher as compared to the parent drug. The AUC and C_{max} ratios of DHD to dydrogesterone are in the order of 40 and 25, respectively. Mean terminal half lives of dydrogesterone and DHD vary between 5 to 7 and 14 to 17 hours, respectively. A common feature of all metabolites characterised is the retention of the 4,6 diene-3-one configuration of the parent compound and the absence of 17α-hydroxylation. This explains the lack of oestrogenic and androgenic effects of dydrogesterone.

- Elimination:

After oral administration of labelled dydrogesterone, on average 63% of the dose is excreted into the urine. Total plasma clearance is 6.4 L/min. Within 72 hours excretion is complete. DHD is present in the urine predominantly as the glucuronic acid conjugate.

- Dose and time dependencies:

The single and multiple dose pharmacokinetics are linear in the oral dose range 2.5 to 10 mg. Comparison of the single and multiple dose kinetics shows that the pharmacokinetics of dydrogesterone and DHD are not changed as a result of repeated dosing. Steady state was reached after 3 days of treatment.

5.3 Preclinical safety data

There are no preclinical safety data of relevance to the prescriber in the target population that are additional to those already included in other sections of the Summary of Product Characteristics (SmPC).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Hypromellose
Maize starch
Colloidal anhydrous silica
Magnesium stearate

Film coat:
Hypromellose
Macrogol 400
Titanium dioxide (E171)
Iron oxides, yellow and red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

PVC/Aluminium blister strips in a printed carton.
Blister packs: 28, 84 or 280 (10 x 28) film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

BGP Products Ltd
Abbott House
Vanwall Business Park
Vanwall Road
Maidenhead SL6 4XE
United Kingdom.

8 MARKETING AUTHORISATION NUMBER

PA2007/009/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 December 2000

Date of last renewal: 21 November 2009

10 DATE OF REVISION OF THE TEXT

May 2016