Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Femoston 2/20 mg tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

This product contains estradiol hemihydrate equivalent to 2 mg estradiol per tablet for the first 14 days of a 28-day cycle (brick-red tablets). For the second 14 days each tablet contains estradiol hemihydrate equivalent to 2 mg estradiol and 20 mg dydrogesterone (blue tablets).

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.
Round, biconvex, brick-red, film-coated tablet with 379 on one side and S on the other side.
Round, biconvex, blue, film-coated tablet with 379 on one side and S on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hormone replacement therapy (HRT) for estrogen deficiency symptoms in menopausal women.

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, special warnings and precautions for use)

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

4.2 Posology and method of administration

Femoston 2/20 is a continuous sequential HRT.
In general, treatment should start with Femoston 1/10. Depending on the clinical response, the dosage can afterwards be adjusted to individual need. If the complaints linked to estrogen deficiency are not ameliorated the dosage can be increased by using Femoston 2/10**.** If either early withdrawal bleeding occurs or if endometrial biopsy reveals inadequate progestational response the dosage can be increased by using Femoston 2/20.

For the first 14 days during a 28-cycle, one tablet containing estradiol is taken daily; during the following 14 days one tablet containing estradiol and dydrogesterone is taken.

After a cycle of 28 days, on the 29th day, a new 28-day cycle begins. This means that the treatment should be taken continuously without a break between packs. Femoston can be taken with or without food.

The days of the week are printed on the back of the blister strips. Firstly the tablets from the part marked with arrow 1 should be taken, then all the tablets from the part marked with arrow 2 should be taken.

Starting Femoston
In women who are not taking hormone replacement therapy, have established amenorrhoea or women who switch from a continuous combined hormone replacement therapy, treatment may be started on any convenient day. In women transferring from a cyclic or continuous sequential HRT regimen, treatment should begin the day following completion of the prior regimen. If the patient is menstruating, treatment is started within five days of the start of bleeding.
If a dose has been forgotten, it should be taken as soon as possible. When more than 12 hours have elapsed, it is recommended to continue with the next dose without taking the forgotten tablet. The likelihood of breakthrough bleeding or spotting may be increased.
For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also section 4.4, Special warnings and precautions for use) should be used.

4.3 Contraindications

Known, past or suspected breast cancer;
Known or suspected estrogen-dependent malignant tumours (e.g. endometrial cancer);
Undiagnosed genital bleeding;
Untreated endometrial hyperplasia;
Previous idiopathic or current venous thromboembolism (deep vein thrombosis, pulmonary embolism);
Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction);
Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal;
Known hypersensitivity to the active substances or to any of the excipients;
Porphyria.

4.4 Special warnings and precautions for use

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

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 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 Femoston, in particular:

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

Reasons for immediate withdrawal of therapy:

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

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

Endometrial hyperplasia

The risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods (see section 4.8, Undesirable effects). The addition of a progestagen for at least 12 days of the cycle in non-hysterectomised women greatly reduces this risk.

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

A randomised placebo-controlled trial, the Womens Health Initiative study (WHI) and epidemiological studies, including the Million Women Study (MWS), have reported an increased risk of breast cancer in women taking estrogens, estrogen-progestagen combinations or tibolone for HRT for several years (see Section 4.8, Undesirable effects).

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

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

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

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

Venous thromboembolism

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

- Generally recognised risk factors for VTE include a personal or family history and severe obesity (BMI>30 kg/m^2) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE.
- Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

- The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all postoperative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT 4 to 6 weeks earlier, if possible. Treatment should not be restarted until the women is completely mobilised.
- If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (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 cardiovascular benefit with continuous combined conjugated estrogens and medroxyprogesterone acetate (MPA).

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

Stroke

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

Ovarian cancer

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

Other conditions

- Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients in Femoston is increased.
- Women with pre-existing hypertriglyceridemia should be followed closely during estrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition.
- Estrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by 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).
- There is no conclusive evidence for improvement of cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined CEE and MPA after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

- 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 (e.g. phenobarbital, phenytoin, carbamezapine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).
- Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones.
- Herbal preparations containing St John's wort (*Hypericum perforatum*) may induce the metabolism of 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 Pregnancy and lactation

Pregnancy:
Femoston is not indicated during pregnancy. If pregnancy occurs during medication with Femoston, treatment should be withdrawn immediately.
Clinically, data based on a large number of exposed pregnancies indicate no adverse effects of dydrogesterone on the foetus.
The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of estrogens and progestagens indicate no teratogenic or foetotoxic effect.

Lactation:
Femoston is not indicated during lactation.

4.7 Effects on ability to drive and use machines

Femoston does not affect the ability to drive or use machines.

4.8 Undesirable effects

Undesirable effects reported in clinical trials and in postmarketing experience are the following:

MedDRA system organ class	*Common >1/100, <1/10*	*Uncommon >1/1,000, <1/100*	*Rare >1/10,000, <1/1,000*	*Very rare <1/10,000 incl. isolated reports*
Infections and infestations		Cystitis-like syndrome, Vaginal candidiasis		
Neoplasms benign, malignant and unspecified		Increase in size of leiomyoma		
Blood and the lymphatic system disorders				Haemolytic anaemia
Psychiatric disorders		Depression, Change in libido, Nervousness		
Nervous system disorders	Headache, Migraine	Dizziness		Chorea
Eye disorders			Intolerance to contact lenses, Steepening of corneal curvature	

Cardiac disorders				Myocardial infarction
Vascular disorders		Hypertension, Peripheral vascular disease, Varicose vein, Venous thromboembolism		Stroke
Gastrointestinal disorders	Nausea, Abdominal pain, Flatulence	Dyspepsia		Vomiting
Hepatobiliary disorders		Gall bladder disease	Alterations in liver function, sometimes with Asthenia or Malaise, Jaundice and Abdominal pain	
Skin and subcutaneous tissue disorders		Allergic skin reactions, Rash, Urticaria, Pruritus		Chloasma or melasma, which may persist when drug is discontinued, Erythema multiforme, Erythema nodosum, Vascular purpura, Angioedema
Musculoskeletal and connective tissue disorders	Leg cramps	Back pain		
Reproductive system and breast disorders	Breast pain/tenderness, Breakthrough bleeding and spotting, Pelvic pain	Change in cervical erosion, Change in cervical secretion, Dysmenorrhoea, Menorrhagia, Metrorrhagia	Breast enlargement, Premenstrual-like symptoms	
Congenital and familial/genetic disorders				Aggravation of porphyria
General disorders and administration site reactions	Asthenia	Peripheral oedema		
Investigations	Increase/decrease in weight			

Breast Cancer

According to evidence from a large number of epidemiological studies and one randomised placebo-controlled trial, the Women's Health Initiative (WHI), the overall risk of breast cancer increases with increasing duration of HRT use in current or recent HRT users.

For *estrogen-only* HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which >80% of HRT use was estrogen-only HRT) and from the epidemiological Million Women Study (MWS) are similar at 1.35 (95%CI 1.21 – 1.49) and 1.30 (95%CI 1.21 – 1.40), respectively.
For *estrogen plus progestagen* combined HRT, several epidemiological studies have reported an overall higher risk for breast cancer than with estrogens alone.

The MWS reported that, compared to never users, the use of various types of estrogen-progestagen combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95%CI: 1.88 – 2.12) than use of estrogens alone (RR = 1.30, 95%CI: 1.21 – 1.40) or use of tibolone (RR=1.45; 95%CI 1.25-1.68).

The WHI trial reported a risk estimate of 1.24 (95%CI 1.01 – 1.54) after 5.6 years of use of estrogen-progestagen combined HRT (CEE + MPA) in all users compared with placebo.

The absolute risks calculated from the MWS and the WHI trials are presented below:

The MWS has estimated, from the known average incidence of breast cancer in developed countries, that:

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

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

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

The WHI trial estimated that after 5.6 years of follow-up of women between the ages of 50 and 79 years, an *additional* 8 cases of invasive breast cancer would be due to *estrogen-progestagen combined* HRT (CEE + MPA) per 10,000 women years.
According to calculations from the trial data, it is estimated that:

- For 1000 women in the placebo group,
    - about 16 cases of invasive breast cancer would be diagnosed in 5 years.
- For 1000 women who used estrogen + progestagen combined HRT (CEE + MPA), the number of *additional* cases would be
    - between 0 and 9 (best estimate = 4) for 5 years' use.

The number of additional cases of breast cancer in women who use HRT is broadly similar for women who start HRT irrespective of age at start of use (between the ages of 45-65) (see section 4.4, Special warnings and precautions for use).'

<u>Endometrial cancer</u>
In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed estrogens. According to data from epidemiological studies, the best estimate of the risk is that for women not using HRT, about 5 in every 1000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65. Depending on the duration of treatment and estrogen dose, the reported increase in endometrial cancer risk among unopposed estrogen users varies from 2-to 12-fold greater compared with non-users. Adding a progestagen to estrogen-only therapy greatly reduces this increased risk.

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

- Estrogen-dependent neoplasms benign and malignant, e.g. endometrial cancer.
- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone replacement therapy users than among non-users. For further information, see section 4.3 Contraindications and 4.4 Special warnings and precautions for use.
- Probable dementia (see section 4.4, Special warnings and precautions for use)

4.9 Overdose

Both estradiol and dydrogesterone are substances with low toxicity. Theoretically, symptoms such as nausea, vomiting, sleepiness and dizziness could occur in cases of overdosing. It is unlikely that any specific or symptomatic treatment will be necessary.
Aforementioned information is applicable for overdosing by children also.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The ATC code is G03FB08. (Estrogens: urogenital system and sex hormones)
Sequential hormone replacement therapy (combined estradiol and dydrogesterone).

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

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.
- Regular withdrawal bleeding with Femoston 1/10 occurred in approximately 75-80% of women with a mean duration of 5 days. Withdrawal bleeding usually started on the day of the last pill of the progestagen phase. Break-through bleeding and/or spotting occurred in approximately 10% of the women; amenorrhoea (no bleeding or spotting) occurred in 10 - 25% of the women per cycle during the first year of treatment.
- With Femoston 2/10, approximately 90% of women had regular withdrawal bleeding. The start day and duration of bleeding, and the number of women with intermittent bleeding was the same as with Femoston 1/10, amenorrhoea occurred in 5 - 15% of the women per cycle during the first year of treatment.
- With Femoston 2/20, approximately 95% of women had regular withdrawal bleeding. The start day and duration of bleeding was the same as with Femoston 1/10 and 2/10. Break-through bleeding and/or spotting occurred in approximately 12% of the women; amenorrhoea occurred in 1 - 7% of the women per cycle during the first year of treatment.

Prevention of osteoporosis.

- Estrogen 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 two years of treatment with Femoston 1/10, the increase in lumbar spine bone mineral density (BMD) was 5.2% ± 3.7% (mean ± SD). The percentage of women who maintained or gained BMD in lumbar zone during treatment was 95%. For Femoston 2/10 and Femoston 2/20 the increase in lumbar spine BMD was 6.6% ± 3.8% (mean ± SD), and the percentage of women with no change or an increase in lumbar spine BMD was 95%.
- Femoston also had an effect on hip BMD. The increase after two years of treatment with 1mg estradiol was 2.7% ± 4.2% (mean ± SD) at femoral neck, 3.5% +/- 5.0% (mean ± SD) at trochanter and 2.7%± 6.7% (mean ± SD) at Wards triangle, after two years of treatment with 2mg estradiol these figures where respectively, 2.6% ± 5.0%; 4.6% ± 5.0% and 4.1% ± 7.4%**.** The percentage of women who maintained or gained BMD in the 3 hip areas after treatment with 1mg estradiol was 67-78% and 71-88% after treatment with 2mg estradiol.

5.2 Pharmacokinetic properties

Orally administered estradiol, comprising particles whose size has been reduced to less than 5 µm, is quickly and efficiently absorbed from the gastrointestinal tract. The primary unconjugated and conjugated metabolites are estrone and estrone sulphate. These metabolites can contribute to the estrogen effect, both directly and after conversion to estradiol. Estrogens are excreted in the bile and reabsorbed from the intestine. During this enterohepatic cycle the estrogens are broken down. Estrogens are excreted in the urine as biologically inactive glucuronide and sulphate compounds (90 to 95%), or in the faeces (5 to 10%), mostly unconjugated. Estrogens are excreted in mothers' milk. The $C_{average}$ is 58 pg/ml, the C_{min} is 44 pg/ml and the C_{max} is 93 pg/ml. The E1/E2 (Estrone/Estradiol) ratio is 5.8.

Dydrogesterone

After oral administration of labelled dydrogesterone, on average 63% of the dose is excreted into the urine. Within 72 hours excretion is complete.

In man, dydrogesterone is completely metabolized. The main metabolite of dydrogesterone is 20α-dihydrodydrogesterone (DHD) and is present in the urine predominantly as the glucuronic acid conjugate. A common feature of all metabolites characterized is the retention of the 4,6 diene-3-one configuration of the parent compound and the absence of 17α-hydroxylation. This explains the absence of estrogenic and androgenic activity.

After oral administration of dydrogesterone, plasma concentrations 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.
Dydrogesterone is rapidly absorbed. The T_{max} values of dydrogesterone and DHD vary between 0.5 and 2.5 hours.

Mean terminal half lives of dydrogesterone and DHD vary between 5 to 7 and 14 to 17 hours, respectively.
The dihydrodydrogesterone $C_{average}$ is 13 ng/ml, the C_{min} is 4.1 ng/ml and the C_{max} is 63 ng/ml. The dydrogesterone $C_{average}$ is 0.38 ng/ml the C_{min} is <0.1 ng/ml and the C_{max} is 2.5 ng/ml.
Dydrogesterone is not excreted in urine as pregnanediol, like progesterone.
Analysis of endogenous progesterone production based on pregnanediol excretion therefore remains possible.

5.3 Preclinical safety data

Supraphysiologically high doses (prolonged overdoses) of estradiol have been associated with the induction of tumours in estrogen-dependent target organs for all rodent species tested characteristic for progesterone-like compounds. *In-vitro* and *in-vivo* data gave no indications of mutagenic effects of dydrogesterone. In long-term studies, doses administered to rats and mice were sufficient to produce hormone-mediated changes, but did not provide tumorogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Hypromellose
Maize starch
Colloidal anhydrous silica
Magnesium stearate

Film Coating
Methylcullulose
Macrogol 400
Quinoline yellow, E104 (blue tablets only)
Patent blue V, E131 (blue tablets only)
Ponceau 4R, E124 (blue tablets only)
Titanium dioxide, E171
Iron oxides red, black and yellow, E172 (brick red tablets only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

The tablets are packed in blister strips of 28. The blister strips are made of PVC film with a covering aluminium foil. Each carton contains 28 tablets.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Solvay Healthcare Limited,
Mansbridge Road
West End,
Southampton SO18 3JD,
England.

8 MARKETING AUTHORISATION NUMBER

PA0108/021/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 October 1997
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10 DATE OF REVISION OF THE TEXT

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