Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Duphaston 10 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 10 mg Dydrogesterone.
Excipients: each tablet contains 111.1 mg of lactose monohydrate.
For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet
A round, biconvex, scored, white film-coated tablet, one side with inscription '155' on either side of the score.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the management of conditions associated with progesterone insufficiency: dysmenorrhoea, endometriosis, infertility, irregular menstrual cycles and pre-menstrual syndrome.

The drug may be used with an estrogen in the management of dysfunctional bleeding or secondary amenorrhoea, or in association with estrogen in hormone replacement therapy.

4.2 Posology and method of administration

Dosages, treatment schedule and duration of treatment may be adapted to the severity of the dysfunction and the clinical response.

Dysfunctional uterine bleeding:
When treatment is started toarrest a bleeding episode Duphaston 10 mg b.d.(twice a day) for five to seven days.

For continuous treatment Duphaston 10 mg b.d. from day 11 to day 25 of the cycle.

Withdrawal bleeding occurs if the endometrium has been adequately primed with either endogenous or exogenous estrogen.

Secondary amenorrhoea:
Duphaston 10 mg b.d. from day 11 to 25 to produce an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen.

Pre-menstrual syndrome:
Duphaston 10 mg b.d. from day 12 to 26 of the cycle. The dosage may be increased if necessary.

Endometriosis:
Duphaston 10 mg two to three times daily from day 5 to 25 of the cycle, or continuously.

Dysmenorrhoea:
Duphaston 10 mg b.d. from day 5 to 25 of the cycle.

Irregular cycles:
Duphaston 10 mg b.d. from day 11 to 25 of the cycle.

Infertility due to luteal insufficiency:
Duphaston 10 mg b.d. from day 11 to 25 of the cycle.Treatment should be maintained for at least three consecutive cycles.

Hormone replacement therapy:
The standard dose is 10 mg Duphaston daily for the last 14 days of each 28-day estrogen treatment cycle. The dose may be increased to 10 mg twice daily if either early withdrawal bleeding occurs, or if endometrial biopsy reveals inadequate progestational response.

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.

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.

Forgotten dose:
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.

There is no relevant use of dydrogesterone before menarche. The safety and efficacy of dydrogesterone in adolescents aged 12-18 years has not been established. Currently available data are described in section 4.8 and 5.1, but no recommendation on a posology can be made.

Method of administration
For oral use.

For administration of higher dosages the tablets should be taken evenly distributed over the day.

4.3 Contraindications

- Known hypersensitivity to the active substances or to any of the excipients.
- Known or suspected progestogen dependant neoplasms (e.g. meningioma).
- Use in patients with undiagnosed irregular vaginal bleeding.
- Contraindications for the use of estrogens should be taken into account when used in combination with dydrogesterone.

4.4 Special warnings and precautions for use

Before initiating dydrogesterone treatment for abnormal bleeding the etiology for the bleeding should be clarified.

Treatment with dydrogesterone has infrequently been associated with alterations in liver function, sometimes accompanied by clinical symptoms. Thus, dydrogesterone should be used with caution in patients with acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal. In cases of severe hepatic impairment treatment should be discontinued.

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.

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 dydrogesterone and ceasing the treatment should be considered:

- Porphyria
- Depression
- Abnormal liver function values caused by acute or chronic liver disease

Other conditions:

Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The following warnings and precautions apply when using dydrogesterone in combination with estrogens for hormone replacement therapy (HRT):

See also the warnings and precautions in the product information of the estrogen preparation.

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, 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 mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Endometrial hyperplasia and carcinoma:
In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods.
The addition of a progestogen such as dydrogesterone cyclically for at least 12 days per month/28 day cycle or continuous combined estrogen-progestogen therapy in non-hysterectomised women can prevent the excess risk associated with estrogen- only HRT.

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

Combined estrogen-progestogen therapy: The randomised placebo-controlled trial, Women's Health Initiative Study (WHI), and a meta-analysis of prospective epidemiological studies, are consistent in finding an increased risk of breast cancer in women taking combined estrogen-progestogen for HRT that becomes apparent after about 3 (1-4) years. Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.

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

Ovarian cancer:
Ovarian cancer is much rarer than breast cancer. Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking estrogen-only or combined estrogen-progestogen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.
Some other studies, including the WHI trial, suggest that use of combined HRT's may be associated with a similar, or slightly smaller, risk.

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.

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.

Generally recognised risk factors for VTE include: use of estrogens, 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 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, dyspnea).

Coronary artery disease (CAD):
There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined estrogen- progestogen or estrogen – only HRT.

Combined estrogen-progestogen therapy: The relative risk of CAD during use of combined estrogen- 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 estrogen – progestogen use is very low in healthy women close to menopause, but will rise with more advanced age.

Ischemic Stroke:
Combined estrogen-progestogen and estrogen- only therapy are associated with an up to 1.5-fold increase in risk of ischemic 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.

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

4.5 Interaction with other medicinal products and other forms of interactions

In vitro data show that the major metabolic pathway generating the main pharmacologically active metabolite 20α dihydrodydrogesterone (DHD) is catalyzed by aldo-keto reductase 1C (AKR 1C) in human cytosol. Next to the cytosolic metabolism there are metabolic transformations by cytochrome P450 iso-enzymes (CYPs), nearly exclusively via CYP3A4, resulting in several minor metabolites. The main active metabolite DHD is substrate for metabolic transformation by CYP3A4. Therefore the metabolism of progestogens and DHD may be increased by concomitant use of substances known to induce CYP enzymes, such as anticonvulsants (eg. phenobarbital, phenytoin, carbamezapine), anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz) and herbal preparations containing e.g., St John's Wort (Hypericum perforatum), sage, or gingko biloba. Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit enzyme-inducing properties when used concomitantly with steroid hormones.
Clinically an increased metabolism of dydrogesterone may lead to decreased effect.
In vitro studies have shown that Dydrogesterone and DHD do not inhibit or induce CYP drug-metabolising enzymes at clinically relevant concentrations.

4.6 Fertility, pregnancy and lactation

Pregnancy
It is estimated that more than 10 million pregnancies have been exposed to dydrogesterone. So far there were no indications of a harmful effect of dydrogesterone use during pregnancy.

Some progestogens have been reported in the literature to be associated with an increased risk of hypospadias. However due to confounding factors during pregnancy, no definitive conclusion can be drawn regarding the contribution of progestogens to

hypospadias.Clinical studies, where a limited number of women were treated with dydrogesterone early in pregnancy, have not shown any increase in risk. No other epidemiological data are hitherto available.

Effects in non-clinical embryo-fetal and post-natal development studies were in line with the pharmacological profile. Untoward effects occurred only at exposures which exceeded the maximum human exposure considerably, indicating little relevance to clinical use (see section 5.3)

Dydrogesterone can be used during pregnancy if clearly indicated.

Breastfeeding
No data exists on excretion of dydrogesterone in mother's milk. Experience with other progestogens indicates that progestogens and the metabolites pass to mother's milk in small quantities. Whether there is a risk to the child is not known. Therefore, dydrogesterone should not be used during the lactation period.

Fertility
There is no evidence that dydrogesterone decreases fertility at therapeutic doses.

4.7 Effects on ability to drive and use machines

Duphaston has a minor influence on the ability to drive and use machines.

Infrequently, dydrogesterone may cause mild somnolence and/or dizziness, especially within the first few hours after intake. Therefore, care should be taken when driving or using machines.

4.8 Undesirable effects

The most commonly reported adverse drug reactions of patients treated with dydrogesterone in clinical trials of indications without estrogen treatment are migraines/headache, nausea, menstrual disorders and breast pain/tenderness.
The following undesirable effects have been observed with the frequencies indicated below during clinical trials using dydrogesterone (n=3483) in indications without estrogen treatment and from spontaneous reporting:

MedDRA system organ class	Common ≥1/100, <1/10	Uncommon ≥1/1,000, <1/100	Rare ≥1/10,000, <1/1,000
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)			Increase in size of progestogen dependent neoplasms (e.g. meningioma)*
Blood and lymphatic system disorders			Haemolytic anaemia*
Immune system disorders			Hypersensitivity
Psychiatric disorders		Depressed mood	
Nervous system disorders	Headache, Migraine	Dizziness	Somnolence
Gastrointestinal disorders	Nausea	Vomiting	

Hepatobiliary disorders		Hepatic function abnormal, (with Asthenia or Malaise, Jaundice and Abdominal pain)	
Skin and subcutaneous tissue disorders		Dermatitis allergic,(e.g. Rash, Urticaria, Pruritus)	Angioedema*
Reproductive system and breast disorders	Menstrual disorders (including metrorhagia, menorrhagia, oligo-/amenorrhoea, dysmenorrhoea and irregular menstruation) Breast pain/tenderness		Breast swelling
Congenital and familial/genetic disorders			Aggravation of porphyria*
General disorders and administration site reactions			Oedema
Investigations		Weight increased	

*Undesirable effects from spontaneous reporting which have not been observed in clinical trials have been attributed to the frequency 'rare' based on the fact that the upper limit of the 95% confidence interval of the frequency estimate is not higher than 3/x where x = 3483 (total number of subjects observed in clinical trials).

Undesirable effects in adolescent population

Based on spontaneous reports and limited clinical trial data, the adverse reaction profile in adolescents is expected to be similar to that seen in adults.

Other adverse reactions have been reported in association with estrogen/progestogen treatment (see section 4.4 and the product information of the estrogen preparation):
- Breast cancer, endometrial hyperplasia, endometrial carcinoma, ovarian cancer
- Venous thromboembolism
- Myocardical infarction, coronary artery disease, ischemic 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 HPRA Pharmacovigilance, Website: www.hpra.ie

4.9 Overdose

Limited data are available with regard to overdose in humans. Dydrogesterone was well tolerated after oral dosing (maximum daily dose taken to date in humans 360 mg).
There are no specific antidotes and treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Genito Urinary system and sex hormones, ATC code: G03 DB01

Dydrogesterone
Dydrogesterone is an orally-active progestogen, which produces a complete secretory endometrium in an estrogen-primed uterus, thereby providing protection for estrogen-induced increased risk of endometrial hyperplasia and/or carcinogenesis. It is indicated in all cases of endogenous progesterone deficiency. Duphaston is non-androgenic, non-estrogenic, non-thermogenic, non-corticoid and non-anabolic.

When used in conjunction with an estrogen, the pharmacodynamic properties relating to the particular estrogen used should also be considered, for example:
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 Duphaston and Estradiol 1mg 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 progestogen 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 Duphaston and Estradiol 2mg, 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 Duphaston and Estradiol 1mg, amenorrhoea occurred in 5 - 15% of the women per cycle during the first year of treatment.

5.2 Pharmacokinetic properties

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 provide pharmacokinetic parameters of dydrogesterone (D) and 20α-dihydrodydrogesterone (DHD) after single dose administration of 10 mg dydrogesterone:

	D	DHD
C_{max} (ng/mL)	2.1	53.0
AUC_{inf} (ng·h/mL)	7.7	322.0

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.

Metabolism:
Following oral administration, dydrogesterone is rapidly metabolized to DHD. The levels of the main active metabolite 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 estrogenic 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

Non-clinical data obtained from conventional studies on single and repeated dose toxicity, genotoxicity and carcinogenic potential reveal no special hazard for humans.

Reproduction toxicity studies in rats have shown an increased incidence of prominent nipples (between day 11 and day 19 of age) and of hypospadias in the male offspring at high dosages not comparable to human exposure. The actual risk of hypospadias in humans cannot be determined in animal studies due to major species differences in metabolism between rats and humans (see also section 4.6)

Limited animal safety data suggest that dydrogesterone has prolongating effects on parturition, which is consistent with its progestogenic activity.

Environmental Risk assessment: Environmental assessment studies have shown that dydrogesterone, may pose a risk to the aquatic environment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose Monohydrate
Maize Starch
Hypromellose
Colloidal Anhydrous Silica
Magnesium Stearate

Film Coating:
Hypromellose
Macrogol 400
Titanium Dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

Cartons of 42 or 60 blister packed tablets in Al/PVC blister strips.
Not all packs sizes may be marketed.

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

This medicinal product may pose a risk to the aquatic environment. Medicines no longer required should not be disposed of via wastewater or household waste. Any unused product or waste material should be disposed of in accordance with local requirements or returned to the pharmacy.

7 MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
Unit 35/36
Grange Parade
Baldoyle Industrial Estate
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2010/010/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 January 1985

Date of last renewal: 28 January 2010

10 DATE OF REVISION OF THE TEXT

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