# *Duphaston* ®

dydrogesterone

Abbott

## 1. NAME OF THE MEDICINAL PRODUCT

Duphaston® 10 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITIVE COMPOSITION

Each film-coated tablet contains 10 mg dydrogesterone.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

A round, biconvex, scored, white, film-coated tablet, one side with inscription '155' on either side of the score (size 7mm).

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutics Indications

- Symptomatic relief of mild to moderate vasomotor symptoms associated with menopause.
- Prevention of postmenopausal osteoporosis, if other treatments are unsuitable.

**Progesterone deficiencies**

- Treatment of dysmenorrhoea.
- Treatment of endometriosis.
- Treatment of secondary amenorrhoea.
- Treatment of irregular cycles.
- Treatment of dysfunction uterine bleeding
- Treatment of threatened miscarriage
- Treatment of habitual miscarriage
- Treatment of infertility due to luteal insufficiency.
- Luteal support as part of an Assisted Reproductive Technology (ART) treatment

### 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.

Symptomatic relief of mild to moderate vasomotor symptoms associated with menopause; prevention of postmenopausal osteoporosis;

- Continuous sequential therapy: An oestrogen is dosed continuously and one tablet of 10 mg dydrogesterone is added for the last 14 days of every 28 day cycle, in a sequential manner.
- Cyclic therapy: When an oestrogen is dosed cyclically with a treatment-free interval, usually 21 days on and 7 days off. One tablet of 10 mg dydrogesterone is added for the last 12 – 14 days of oestrogen therapy.

If ultrasound or endometrial biopsies would reveal inadequate progestational response, 20 mg dydrogesterone should be prescribed.

Dysmenorrhoea:
10 mg twice daily from day 5 to day 25 of the menstrual cycle.

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

Dysfunctional bleeding (to arrest bleeding):
10 mg twice daily for five to seven days. Duphaston® should be given with oestrogen.

Dysfunctional bleeding (to prevent bleeding):
10 mg twice daily from day 11 to day 25 of the cycle. Duphaston® should be given with oestrogen.

Amenorrhoea:
An oestrogen once daily from day 1 to day 25 of the cycle, together with 10 mg dydrogesterone twice daily from day 11 to day 25 of the cycle.

Irregular cycles:
10 mg twice daily from day 11 to day 25 of the cycle.

Threatened miscarriage:
40 mg at once, then 10 mg every eight hours until symptoms remit.

Habitual miscarriage:
10 mg twice daily until the twentieth week of pregnancy.

Infertility due to luteal insufficiency:
10 mg daily from day 14 to day 25 of the cycle. The treatment should be continued for at least 6 consecutive cycles. It is advisable to continue this treatment during the first months of any pregnancy using the doses stated with respect to habitual miscarriage.

Luteal support as part of an Assisted Reproductive Technology (ART) treatment
10 mg three times daily (30 mg daily) starting at the day of oocyte retrieval and continuing for 10 weeks if pregnancy is confirmed.

There is no relevant use of dydrogesterone before menarche. The safety and efficacy of dydrogesterone in adolescents aged 12 to 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 substance or to any of the excipients.
- Known or suspected progestogen dependent neoplasms (e.g. meningioma)
- Undiagnosed vaginal bleeding
- Treatment for luteal support as part of an Assisted Reproductive Technology (ART) treatment should be discontinued upon diagnosis of abortion/miscarriage.
- Contraindications for the use of estrogens when used in combination with dydrogesterone.
- Existence of serious liver disorders, or serious liver disorders in the medical history as long as the liver function values have not normalised

**4.4 Special warnings and precautions for use**

Before initiating dydrogesterone treatment for dysfunctional uterine bleeding, an organic cause must be ruled out.

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

If any of the following disorders occurs for the first time or worsens during use, discontinuation of the treatment must be considered:
- Exceptionally severe headache, migraine or symptoms which might suggest cerebral ischaemia
- A notable rise in blood pressure
- Occurrence of venous thromboembolism

In cases of habitual and threatened miscarriage, the viability of the foetus should be determined and checked during treatment to see if the pregnancy is continuing and whether the embryo is still alive.

Conditions which need monitoring

It is known that the following rare conditions can be influenced by sex hormones, and during pregnancy or during the use of sex hormones may occur or worsen: cholestatic jaundice, herpes gestationis, severe pruritus, otosclerosis and porphyria.

Patients with a history of depression should be monitored carefully. If severe depression recurs, the treatment with dydrogesterone must be stopped.

Other conditions

Patient 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 oestrogens for hormone replacement therapy (HRT):

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

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

Medical examination / follow-up

Before initiating or re-instituting hormone replacement therapy (HRT), a complete medical history (including family history) should be taken. Physical (including gynaecological and mammary) examinations should be guided by the history and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature suited to each individual woman. Women should be advised what changes in their breasts should be reported to their doctor (see 'Breast cancer' below).

Investigations, including imaging procedures, e.g., mammography, should be carried out in accordance with the applicable screening guidelines, taking into account the medical situation of the individual woman.

Endometrial hyperplasia and carcinoma

In women with an intact uterus, the risk of endometrial hyperplasia and carcinoma is increased with long-term use of oestrogens without the addition of progestogen. Depending on the duration and the oestrogen dose, the risk is 2 to 12 times higher than in women who do not take any oestrogen. After stopping the oestrogen treatment, the risk remains for at least 10 years. This additional risk can be prevented by combining the oestrogen therapy for at least 12 days per month/28-day cycle with a progestogen, such as dydrogesterone.

Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting occur after taking the therapy for some time or if they continue after the treatment has ended, further investigation is then indicated. This may mean that an endometrial biopsy should be carried out so as to be able to rule out malignancy.

Breast cancer

All available data showed an increased risk of breast cancer if women take combined estrogen-progestogen or estrogen-only HRT. This risk is dependent on the duration of its use.

*Combined treatment with oestrogen and progestogen:*

The randomized, 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 after about 3 (1-4) years of use. 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 treatment, especially combined oestrogen and progestogen treatment, increases the density of the 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 study, suggest that the use of combined HRTs may be associated with a similar, or slightly smaller, risk.

Venous thromboembolism

HRT is associated with a 1.3 to 3 times greater risk of developing venous thromboembolism (VTE), i.e., deep vein thrombosis or pulmonary embolism. The possibility of this occurring is greater in the first year of HRT than later.

Patients with known thrombophilia have an increased risk of VTE and HRT may add to this risk. HRT is therefore also contraindicated in these patients.

Generally recognized risk factors for VTE include the use of oestrogens, older age, major surgery, prolonged immobilization, 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.

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

In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counseling regarding its limitations (only a proportion of thrombophilic defects are identified by screening). If a thrombopihilic defect is identified which has led to 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 should carefully weigh the benefits and risks of using HRT.

If VTE develops after initiating therapy, the drug should be discontinued. Patient should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. pain swelling of a leg, sudden pain in the chest, dyspnea).

Coronary artery disease (CAD)

There is no evidence from randomized 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 women close to menopause, but will rise with more advanced age.

Ischaemic stroke
Use of combined HRT or HRT using oestrogen alone is associated with a 1 to 1.5 times greater 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 absolute risk of stroke will increase with age.

Excipients:
This medicinal product contains Lactose monohydrate. 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**

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 isoenzymes (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 dydrogesterone and DHD may be increased by concomitant use of substances known to induce these CYP enzymes such as anticonvulsants (e.g. Phenobarbital, phenytoin, carbamazepine), 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 cytochrome enzyme inhibitors, by contrast exhibit enzyme-inducing properties when used concomitantly with steroid hormones.

Clinically, increased metabolism of dydrogesterone may lead to a decreased effect and changes in the bleeding pattern.

In vitro studies have shown that dydrogesterone and DHD do not inhibit or induce CYP drug-metabolizing 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 literature to be associated with an increased risk of hypospdias. 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 exist 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 dose.

**4.7 Effects on ability to drive and use machines**
Dydrogesterone has 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 oestrogen treatment are vaginal haemorrhage, migraines / headache, nausea, vomiting, abdominal pain, 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 oestrogen treatment, in two company sponsored interventional clinical trials in luteal support as part of an ART treatment using dydrogesterone (n=1036) and from spontaneous reporting. Frequencies are based on the most conservative approach.

| MedDRA system organ class | Very common ≥1/10 | Common ≥1/100, <1/10 | Uncommon ≥1/1,000, <1/100 | Rare ≥1/10,000, <1/1,000 |
|---|---|---|---|---|
| Neoplasms benign, malignant and unspecified (incl. systs and polyps) | | | | Increase in size of progestogen dependent neoplasms (e.g., meningioma)* |
| Blood and the lymphatic system disorders | | | | Haemolytic anaemia* |
| Psychiatric disorders | | | Depressed mood | |
| Immune system | | | | Hypersensitivity |
| Nervous system | | Migraines / headache | Dizziness | Somnolence |
| Gastrointestinal disorders | | Nausea, Vomiting, Abdominal pain | | |
| Hepatobiliary disorders | | | Hepatic function abnormal (with jaundice, asthenia or malaise, and abdominal pain) | |
| Skin and subcutaneous tissue disorders | | | Dermatitis allergic (e.g. rash, pruritus, urticaria) | Angioedema* |
| Reproductive system and breast disorders | Vaginal haemorrhage | Menstrual disorders (including metrorrhagia, menorrhagia, oligo-/amenorrhoea, dysmenorrhoea and irregular menstruction) | | Breast swelling |

| | | | | |
|---|---|---|---|---|
| | | Breast pain / tenderness | | |
| General disorders and administration site conditions | | | | 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.

Undesirable effects that are associated with an oestrogen-progestogen treatment (see also section 4.4 and the product information of the oestrogen preparation):
- Breast cancer, endometrial hyperplasia, endometrial carcinoma, ovarian cancer
- Venous thromboembolism
- Myocardial infarction, coronary artery disease, ischemic stroke

### 4.9 Overdose

Symptoms
Dydrogesterone is a drug of very low toxicity. Nausea, vomiting, somnolence and dizziness are symptoms that theoretically may occur in the event of an overdose. There are no known cases where an overdose of dydrogesterone has resulted in harmful consequences.

Treatment
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: G03DB01

Mechanism of action
Dydrogesterone is an orally-active progestogen which produces a complete secretory endometrium in an oestrogen-primed uterus thereby providing protection against the increased risk for endometrium hyperplasia and/or carcinogenesis induced by oestrogens. It is indicated in all cases of endogenous progesterone deficiency. Dydrogesterone has no oestrogenic, no androgenic, no thermogenic, no anabolic and no corticoid activity.

Clinical efficacy and safety

Lotus I and Lotus II clinical study(s) confirmed the following:

A Double-Blind, Double-Dummy, Randomized, Two-arm, Multicenter Study Comparing the Efficacy, Safety, and Tolerability of Oral Dydrogesterone 30 mg daily versus Intravaginal Micronized Progesterone Capsules 600 mg daily for Luteal Support in In-Vitro Fertilization (LOTUS I).

A Randomized, Open-label, Two-arm, Multicenter Study Comparing the Efficacy, Safety and Tolerability of Oral Dydrogesterone 30 mg daily versus Crinone 8% intravaginal progesterone gel 90 mg daily for Luteal Support in In Vitro Fertilization (LOTUS II).

The primary objective of non-inferiority of oral dydrogesterone compared to intravaginal micronized progesterone in terms of the presence of fetal heartbeats at 12 weeks gestation (10 weeks pregnancy) was achieved.

In the studied patient population, pregnancy rates at 12 weeks' gestation (pregnancy week 10) were 37.6% and 33.1% (LOTUS I) and 36.7% and 34.7% (LOTUS II)~~.~~, for oral dydrogesterone and micronized vaginal progesterone respectively. The difference in the pregnancy rate between the two groups was 4.7 (95%CI, -1.2; 10.6) (LOTUS I) and 2.0 (95%CI, -4.0; 8.0) (LOTUS II).

Within the safety sample of 1029 subjects (LOTUS I) and 1030 subjects (LOTUS II) with at least one dose of study medication administered, the incidence of the most frequently reported TEAE was similar between the two treatment groups.

Due to the nature of the studied patient population/indication a number of early abortions/miscarriages are expected; especially until 12 weeks' gestation (pregnancy week 10) as the expected pregnancy rate at this time point is about 35%.

The safety profile observed both LOTUS studies is as expected taking into account the well-established safety profile of dydrogesterone and the treatment population/indication.

**5.2 Pharmacokinetic properties**

Absorption:
Following oral administration, dydrogesterone film-coated tablets is rapidly absorbed. Maximum plasma concentration of about 3.2ng/ml and 57ng/ml are attained between 0.5 and 1.5 hours after dosing for the parent drug dydrogesterone and its active metabolite 20α-dihydrodydrogesterone (DHD) respectively. The total drug exposures across time (AUC) are about 9.1 and 220 ng.hr/ml for Dydrogesterone and DHD respectively.

After a single dose, food delays the peak plasma concentration of dydrogesterone with approximately 1 hour, resulting in approximately 20% lower dydrogesterone peak plasma concentrations without affecting the extent of exposure to dydrogesterone and DHD.

The observed effect of concomitant food intake on the peak plasma concentration of dydrogesterone is considered not clinically relevant. Therefore, Duphaston® film-coated tablets can be taken without regards to food.

Distribution:
After oral administration of dydrogesterone the apparent volume of distribution is large, being approximately 22,000 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 at similar times as Dydrogesterone. The plasma levels of DHD are substantially higher as compared to the parent drug. The AUC and Cmax ratios of DHD to dydrogesterone are approximately 25 and 20, respectively. The mean terminal elimination half lives of both dydrogesterone and DHD is about 15 hours.

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 lack of estrogenic and androgenic effects of dydrogesterone.

Elimination:
After oral administration of labeled dydrogesterone, on average 63% of the dose is excreted into the urine. The apparent total body clearance of dydrogesterone from plasma is high at approximately 20L/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 of 2.5 to 20 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 conditions are generally 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.

## 6. PHARMACEUTICAL PARTICULARS

**6.1 List of excipients:**

Core:
Lactose monohydrate,
Hypromellose,
Maize starch,
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**
Store in a dry place, not below $0^{o}$C or above $30^{o}$C in the original package.
Keep the tablets out of the reach of children.

**6.5 Nature and contents of container**
Blister strip of aluminium foil and PVC film, uncoated or coated with PVDC, of 20 tablets.

**6.6 Special precautions for disposal**
Any unused product or waste material should be disposed of in accordance with local requirements.

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**for**
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