DUPHASTON® (Dydrogesterone)
10mg Film Coated Tablets

COMPOSITION
Dydrogesterone U.S.P. 10mg.

DESCRIPTION
Dydrogesterone is an orally active progestogen which produces a complete or partial inhibition of an estrogen-stimulated endometrium thereby providing protection for oestrogen induced increased risk for endometrial hyperplasia and/or carcinoma. It is indicated in a number of endocrine cycle deficits. Dydrogesterone has no estrogenic, no androgenic, no thymogenic, no anabolic and no corticoid activity.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic
Gluconic Uronic system and sex hormones.
Dydrogesterone is an orally active progestogen which produces a complete secretary endometrium in an estrogen-stimulated uterus thereby providing protection for endometrial hyperplasia and/or carcinoma. It is indicated in all cases of endocrine cycle deficits. Dydrogesterone has no estrogenic, no androgenic, no thymogenic, no anabolic and no corticoid activity.

PHARMACOKINETICS
After oral administration of labelled dydrogesterone on average 63% of the dose is excreted into the urine. Within 72 hours excretion is complete. Oral absorption is completely metabolised. The main metabolite of dydrogesterone is 20α-dydroxy-4-dehydroprogesterone (DHD) and is present in the urine predominantly as the glucuronide acid conjugate. A common feature of all metabolites characterized is the retention of the 20α-hydroxy group, in the parent compound and the absence of 17α-hydroxylation. This explains the lack of estrogenic and androgenic effects of dydrogesterone. After oral administration of dydrogesterone, plasma concentrations of DHD are proportional to the dose of the drug. The AUC and Cmax ratios of DHD to dydrogesterone are in the order of 150 and 130, respectively. Dydrogesterone is rapidly absorbed. The T values of max dydrogesterone and DHD vary between 0.5 and 2.5 hours. Mean terminal half-life of dydrogesterone and DHD vary between 5 to 7 and 14 to 17 hours respectively. Dydrogesterone is not excreted in the urine. The analysis of endogenous progesterone production based on progandiol excretion therefore remains possible.

INDICATIONS
Hormone replacement therapy
To counteract the premature cessation of oestrogen in the endometrium or hormone replacement therapy for women with disorders due to natural or surgical induced menopause with an intact uterus.

Progesterone deficiencies
Treatment of progesterone deficiencies such as:
- Treatment of dysmenorrhoea
- Treatment of endometriosis
- Treatment of secondary amenorrhoea
- Treatment of irregular cycles
- Treatment of dysfunctional uterine bleeding
- Treatment of pre-menstrual syndrome
- Treatment of threatened and habitual abortion, associated with proven progesterone deficiency
- Treatment of endometriosis thereby providing protection for estrogen induced increased risk for endometrial hyperplasia and/or carcinoma

DOSAGE AND ADMINISTRATION
Dosages, treatment schedule and duration of treatment may be adjusted to the severity of the condition and the clinical response.

Dysmenorrhoea: 10 or 20mg dydrogesterone per day from day 5 to 25 of the menstrual cycle.

Endometriosis: 10 to 30mg dydrogesterone per day from day 5 to 25 of the menstrual cycle.

Premenstrual syndrome: 10 mg dydrogesterone twice daily starting with the second half of the menstrual cycle until the first day of the next cycle.

Irregular cycles: 10 or 20 mg dydrogesterone per day starting with the second half of the menstrual cycle until the first day of the next cycle. The starting day and the number of treatment days will depend on the individual cycle length.

Threatened abortion: An initial dose of up to 40 mg dydrogesterone may be given during the first trimester of pregnancy, followed by a single daily dose of 10 mg dydrogesterone twice daily starting with the second half of the menstrual cycle until the first day of the next cycle. Treatment should be maintained for at least three consecutive cycles.

Continuous sequential therapy:
- For continuous treatment, 10 or 20 mg dydrogesterone per day, to arrest a bleeding episode, 20 or 30 mg dydrogesterone per day is to be given during the first 25 days of the cycle, or continuously.

Other conditions
- Endometrial hyperplasia
- Ovarian cancer
- Breast cancer

Cyclic therapy:
When an estrogen 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 estrogen therapy.

Depending on the clinical response, the dosage can subsequently be adjusted to 20 mg dydrogesterone per day.

There is no relevant use of dydrogesterone before menarche. The safety and efficacy of dydrogesterone in adolescents age 12-18 years has not been established. Currently available data are described in section 4.4 and 5.1, but no recommendation on a posology can be made.

CONTRAINDICATIONS
- Hypersensitivity to the active substance or any of the excipients
- Known or suspected progesterone dependent neoplasms (e.g. meningiomas)
- Undiagnosed vaginal bleeding
- If used to prevent endometrial hyperplasia (in women using estrogen). Contraindication for use of estrogens in combination with progesterogens, such as Dydrogesterone.

WARNINGS AND SPECIAL PRECAUTIONS FOR USE
Before initiating dydrogesterone treatment for abnormal bleeding the etiology for the bleeding should be clarified. Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting occurs at 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 concomitant hormone replacement therapy. Information on these should be given to the patient so that they may be taken into account at any time during treatment.

- Prophylaxis
- Abnormal liver function values caused by acute or chronic liver disease

Other conditions
- Patients with new hereditary problems of glucose intolerance.
- Large lactate deficiency or glucosoinulin multishock should not take the 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.

Treatment for the postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In some 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 is 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 favorable than in older women.

Medical examinations; Follow-up.
Before initiating or resuming HRT, a complete personal and family medical history should be taken. Physical including physical and breast) examination should be guided by this and by 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.

Endometrial hyperplasia
- Long-term use of oestrogen without addition of progestogens increases the change of endometrial hyperplasia and endometrial carcinoma in women with a uterus. This risk may largely be prevented by combining the oestrogen therapy for at least 12 days per cycle with a progestogen, such as dydrogesterone.

Cancer
- Breast cancer

The overall evidence suggests an increased risk of breast cancer in women taking combined estrogen-progesterogen and possibly also estrogen-only, HRT that is, dependent on the duration of taking HRT. Combined estrogen-progesterogen therapy has been shown to cause a randomized placebo-controlled trial. Women’s Health Initiative study (WHI), and epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined estrogen-progesterogen for HRT that becomes apparent after about 5 years. The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment. HRT, especially estrogen-progesterone combined treatment, increases the density of mammographic images which may adversely affect the detection of breast cancer.

Ovarian cancer
- Chorion cancer is much more than breast cancer.

Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking estrogen-only or combined estrogen-progesterogen HRT, which becomes apparent within 5 years of use and decreases again over time after stopping. Some other studies including the WHI trial suggest that use of combined estrogen-only HRT may be associated with a similar, or slightly smaller, risk.

Venous thrombo-embolism
- HRT is associated with a 1.3-3 fold risk of developing venous thrombo-embolism (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. Generally recognized risk factors for VTE include, use of estrogens, older age, major surgery, prolonged immobilization, obesity (BMI >30 kg/m2), pregnancy, postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of venous varicose veins in VTE.

As all postmenopausal patients, prophylactic measures need 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 mobilised. Women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be altered after careful counseling regarding risks and benefits.
**UNDESIRABLE EFFECTS**

- 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 in whom HRT will increase with age.

- This medicinal product contains Lactose monohydrate. Patients with rare hereditary problems of glucose metabolism, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

- KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

**INTERACTIONS**

- Interactions with other medicinal products and other forms of interaction. In vitro data show that the major metabolic pathway generating the main pharmacologically active metabolite 20β-dihydroxyprogesterone (DHP) is catalyzed by the human enzyme 1C (1C11/1). The metabolism of dydrogesterone is mediated by CYP3A4 in human liver. Therefore, the metabolism of dydrogesterone and 'DHP may be increased by concomitant use of substances known to induce CYP enzymes such as rifampicin, phenytoin, carbamazepine, or -blockers. Even if the concomitant use of such substances is necessary, a dose reduction of dydrogesterone may be indicated. On the other hand, the pharmacokinetics of dydrogesterone are not altered by the use of oestrogens or progestins. The metabolism of dydrogesterone and DHP may be decreased by concomitant use of substances known to inhibit CYP enzymes such as the macrolides (e.g., erythromycin, clarithromycin, azithromycin), HMG-CoA reductase inhibitors (e.g., lovastatin, simvastatin), or the protease inhibitors (e.g., saquinavir, indinavir). In such cases, the dose of dydrogesterone may have to be increased. However, the clinical significance of the pharmacokinetic interaction is unknown. No drug interactions with herbal preparations containing St John's Wort (Hypericum perforatum) have been reported.

- Drug interactions with herbal remedies: Some progestogens have been reported in the literature to be associated with an increased risk of hormone-related effects. In particular, the use of St John's Wort (Hypericum perforatum) has been associated with a decrease in the effect of estrogen therapy. However, further studies are needed to determine the clinical significance of this interaction.

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**MORE INFORMATION**

- Information in this leaflet is limited. Further information is available on request.

- To be sold on the prescription of a registered medical practitioner only.

- Keep all medicines out of the reach of children.

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**PREGNANCY**

- It is estimated that more than 10 million pregnancies have been exposed to dydrogesterone. For the majority of women, there were no indications of a harmful effect of dydrogesterone use during pregnancy. However, some progestogens have been reported in the literature to be associated with an increased risk of hormone-related effects. In particular, the use of St John's Wort (Hypericum perforatum) has been associated with a decrease in the effect of estrogen therapy. However, further studies are needed to determine the clinical significance of this interaction.

**FERTILITY**

- There is no evidence that dydrogesterone decreases fertility at levels that are metabolically inactive. However, it is not known whether dydrogesterone may affect fertility in the absence of estrogen therapy. Further studies are needed to determine the clinical significance of this interaction.

**BREASTFEEDING**

- No data exist on the excretion of dydrogesterone in human 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.

**OVERDOSE**

- Limited data are available with regard to overdosage in humans. Dydrogesterone was well tolerated after oral dosage (maximum daily dose of 100 mg) and no toxic symptoms were observed in animals. The symptoms of overdosage are nausea, vomiting, diarrhea, and general abdominal discomfort. Treatment should be symptomatic.

**STORAGE**

- Store below 25°C in a dry place. Protect from light.

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**PRESENTATION**

- Duphaston 10 mg film-coated tablets: Blister pack of 24 tablets. (List No. W 156)

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