Duphaston®
(Dydrogesterone)
10mg Film Coated Tablets

COMPOSITION
Duphaston 10mg tablets: Each film coated tablet contains Dydrogesterone U.S.P. ..... 10mg.
Excipient(s) with known effect: Each tablet contains 111.1 mg Lactose monohydrate

DESCRIPTION
Dydrogesterone is an orally-active progestogen which produces a complete secretory endometrium in an oestrogen-primed uterus thereby providing protection for oestrogen induced increased risk for endometrium hyperplasia and/or carcinogenesis.
Dydrogesterone has no oestrogenic, no androgenic, no thermogenic, no anabolic and no corticoid activity.
Excipients: Lactose monohydrate, Hypromellose, maize starch, colloidal anhydrous silica, magnesium stearate, Opadry Y-1-7000 hite (hypromellose, macrogol 400, titanium dioxide (E171)).

PHARMACOLOGICAL PROPERTIES
Pharmacodynamics
Pharmacotherapeutic group: Genito Urinary system and sex hormones
Dydrogesterone is an orally-active progestogen which produces a complete secretory endometrium in an oestrogen-primed uterus thereby providing protection for estrogen induced increased risk for endometrium hyperplasia and/or carcinogenesis. It is indicated in all cases of endogenous progesterone deficiency. Dydrogesterone has no estrogenic, no androgenic, no thermogenic, 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. Dydrogesterone is completely metabolized. The main metabolite of dydrogesterone is 20a-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 17a-hydroxylation. This explains the lack of estrogenic and androgenic effects of dydrogesterone. After oral administration of dydrogesterone, plasma concentrations of DHD are substantially higher as compared to the parent drug. The AUC and Cmax ratios of DHD to dydrogesterone are in the order of 40 and 25 respectively. Dydrogesterone is rapidly absorbed. The T values of max dydrodesterone 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. Dydrogesterone is not excreted in urine as pregnanediol, like progesterone. Analysis of endogenous progesterone production based on pregnanediol excretion therefore remains possible.

INDICATIONS
Hormone replacement therapy
To counteract the effects of unopposed oestrogen on the endometrium in 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 infertility due to luteal insufficiency

DOSAGE AND ADMINISTRATION
Dosages, treatment schedule and duration of treatment may be adapted to the severity of the dysfunction and the clinical response.
Dysmenorrhoea: 10 or 20mg mg dydrogesterone per day from day 5 to day 25 of the menstrual cycle.

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

Dysfunctional uterine bleeding: When treatment is started to arrest a bleeding episode, 20 or 30 mg dydrogesterone per day is to be given for up to 10 days.
For continuous treatment, 10 or 20 mg dydrogesterone per day should be given during the second half of the menstrual cycle. The starting day and the number of treatment days will depend on the individual cycle length.
Withdrawal bleeding occurs if the endometrium has been adequately primed with either endogenous or exogenous estrogen.

Secondary amenorrhoea: 10 or 20 mg dydrogesterone per day, to be given daily for 14 days during the second half of the theoretical menstrual cycle to produce an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen.

Pre-menstrual syndrome: 10 mg dydrogesterone twice daily 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.

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 followed by 20 or 30mg per day until symptoms remit.
Habitual abortion: 10 mg dydrogesterone twice daily until the twelfth week of pregnancy.
Infertility due to luteal insufficiency: 10 or 20 mg dydrogesterone 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.
Hormone replacement therapy:
Continuous sequential therapy: An estrogen 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 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 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.

CONTRAINDICATIONS
- Hypersensitivity to the active substance or to any of the excipients.
- Known or suspected progestogen dependent neoplasms (e.g. meningioma)
- Undiagnosed vaginal bleeding
- If used to prevent endometrial hyperplasia (in women using estrogens): Contraindications for use of oestrogens in combination with progestagens, 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 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 glucosegalactose 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, however, the balance of benefits and risks for these women may be more favorable than in older women.
Medical examination / follow-up
Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see 'Breast cancer' below).
Investigations, including appropriate imaging tools, e.g., mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.
Endometrial hyperplasia
- Long-term use of oestrogens without addition of progestagens 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 progestagen, such as dydrogesterone.

Breast cancer
- The overall evidence suggests an increased risk of breast cancer in women taking combined estrogen-progestogen and possibly also estrogen-only HRT, that is dependent on the duration of taking HRT. Combined estrogen-progestogen therapy: The 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-progestogen for HRT that becomes apparent after about 3 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-progestogen combined treatment, increases the density of mammographic images which may adversely affect the detection of breast cancer.

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

Venous thrombo-embolism
- 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 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 varicose veins in VTE.
  As in all postoperative 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 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

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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 chronic 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 randomized 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 estrogenprogestogen 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.

Cerebrovascular accident (CVA)

- 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, the Lapp lactase deficiency or glucosegalactose malabsorption should not take this medicine.

INTERACTIONS

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 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 dydrogesterone and DHD may be increased by concomitant use of substances known to induce 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), valerian root, 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, an increased metabolism of dydrogesterone may lead to a decreased effect. In vitro studies have shown that dydrogesterone and DHD do not inhibit or induce CYP drug metabolizing enzymes at clinically relevant concentrations.

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.

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.

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.

UNDESIRABLE EFFECTS

Like all medicines, Duphaston may have side effects. If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

The frequencies of study related adverse events are ranked according to the following: common (frequency 1.10%), uncommon (frequency <1%), rare (frequency <0.1%), very rare (frequency <0.01%), including isolated reports.

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)			In crease in size of progestogen dependent neoplasms (e.g., meningioma)*
Blood and the lymphatic system disorders			Haemolytic anaemia*
Psychiatric disorders		Depressed mood	
Immune system disorders			Hypersensitivity
Nervous system disorders	Migraines/ headache	Dizziness	Somnolence
Gastrointestinal disorders	Nausea	Vomiting	
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	Menstrual disorders (including metrorrhagia, menorrhagia, oligo-/amenorrhoea, dysmenorrhoea and irregular menstruation) Breast pain/ tenderness		Breast swelling
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 estrogen-progestogen treatment (see product information of the estrogen preparation):

- Breast cancer, endometrial hyperplasia, endometrial carcinoma, ovarian cancer
- Venous thromboembolism
- Myocardial infarction, coronary artery disease, ischemic stroke

OVERDOSAGE

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). No reports of ill-effects from overdose have been recorded. If a large overdose is discovered within two or three hours and treatment seems desirable, gastric lavage is recommended. There are no specific antidotes and treatment should be symptomatic.

STORAGE

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

PRESENTATION

Duphaston 10 mg film coated tablets:
Blister pack of 2 x 10 tablets. (List No. W 156)

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.

ڈوفاسٹن®

(ڈائیڈروجیسٹیرون) ۱۰ ملی گرام فلم کوٹڈ گولیاں

پیشکش: ۱۰ ملی گرام ڈائیڈروجیسٹیرون (یو۔ایس۔پی) فلم کوٹڈ ۲۰ گولیاں بلسٹر پیک میں دستیاب ہیں۔

علامات:

۱۔ وہ خواتین جن میں قدرتی طور پر یا جراحی کے عمل کے نتیجہ میں سن یاس شروع ہو چکا ہو اور اُن کا رحم بھی سالم حالت میں ہو اُن خواتین میں جب ایچ آر ٹی تجویز کی جاتی ہے تو ایسٹروجن کے اثر کو متوازن کرنے کے لیے۔
۲۔ ڈوفاسٹن اُن حالتوں میں تجویز کی جاتی ہے۔ جہاں اینڈومیٹریوسس پر پروجیسٹرون کی کمی کا اندیشہ ہو۔

ڈوفاسٹن مندرجہ ذیل حالتوں میں موثر ثابت ہوئی ہے۔

- تکلیف دہ حیض کی صورت میں
- اسقاطِ حمل کے خدشے کی صورت میں
- رکی حیض کی صورت میں
- ضمنی بے حیض کی صورت میں
- بے محلی دورِ رحم کی صورت میں
- پی۔ایم۔ایس
- بانجھ پن
- بے قاعدہ حیض کی صورت میں

عمومی خوراک: ۱۰ ملی گرام کی گولی دن میں دو دفعہ۔ مرض کی نوعیت کے پیشِ نظر خوراک کو مزید بڑھایا جا سکتا ہے۔ خوراک کی ترتیب ایک ممکن طریقے سے پورے دن میں تقسیم کی جانی چاہیے۔

ممانعت: دوائی کے کسی بھی جزو کے ساتھ حساسیت۔

حاملہ اور دودھ پلانے والی خواتین: اب تک اس بات کی کوئی شہادت نہیں ہے کہ ڈوفاسٹن حاملہ خواتین کے لئے نامزوں ہے۔ ڈوفاسٹن دودھ کے ذریعے خارج ہوتی ہے۔

مُضر اثرات: ڈوفاسٹن کے ساتھ کوئی مُضر اثرات نہیں پائے گئے۔ کچھ مریضوں میں خون کا دھبا لگنے کی شکایت پیدا ہو سکتی ہے۔ جو کہ دوا کی مقدار بڑھانے سے دور ہو جاتی ہے۔

صرف مستند ڈاکٹر کے نسخے کے مطابق ہی دوا فروخت کی جائے۔

تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

دوا کو 25°C سے کم درجہ حرارت پر نمی اور روشنی سے محفوظ رکھیں۔

Manufactured by:
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17.5 K.M. Multan Road, Lahore.

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