Duphaston® 10 mg

film-coated tablets

10 mg dydrogesterone

Abbott

Read all of this leaflet carefully before you start taking this medicine.
Keep this leaflet. You may need to read it again. If you have questions not answered by this pamphlet, please ask your doctor or pharmacist. This medicine has been prescribed to you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

Duphaston is a round, biconvex, scored, white coloured film -coated tablet for oral administration, one side of the tablet with the inscription '155' on either side of the break mark. Each tablet contains 10 mg of dydrogesterone
The score line is present only to facilitate breaking the tablet into two halves for ease of swallowing and is not intended to divide the tablet into two equal doses.

Excipients (nonmedicinal ingredients):
Tablet core:
Lactose monohydrate, hypromellose, maize starch, colloidal anhydrous silica, magnesium stearate

Film-Coating:
Hypromellose, macrogol 400, titanium dioxide (E171)

Indications
Hormone replacement therapy
Duphaston is indicated to counteract the effects of unopposed oestrogen on the endometrium (inner lining of the uterus) in hormone replacement therapy for women with disorders due to naturally or surgically induced menopause with an intact uterus.

Progesterone deficiencies
Duphaston is indicated for the treatment of progesterone deficiencies such as:
- Treatment of dysmenorrhoea (painful menstruation)
- Treatment of endometriosis (growth of uterine tissues outside the uterus with associated symptoms)
- Treatment of secondary amenorrhoea (cessation of menstruation)
- Treatment of irregular cycles
- Treatment of dysfunctional uterine bleeding
- Treatment of premenstrual syndrome
- Treatment of threatened and habitual abortion, associated with proven progesterone deficiency
- Treatment of infertility due to luteal (ovarian yellow body) insufficiency

Dosage and administration
Always take Duphaston exactly as your doctor has prescribed. If you have any questions, contact your doctor or pharmacist.

If you forget to take your tablet(s), do not take a double dose to compensate for it. If you require further information, please ask your doctor or pharmacist for advice.

For hormone replacement therapy:
- In combination with continuous oestrogen therapy, take one tablet daily for 14 consecutive days of a 28 day cycle.
- In combination with cyclical oestrogen therapy, take one tablet daily during the last 12 to 14 days of oestrogen therapy.
- For doctors: If endometrial biopsies or ultrasound reveal inadequate progestational response, 20 mg dydrogesterone should be prescribed.

If you are not sure what type of oestrogen therapy you are on, talk to your doctor before taking Duphaston.

Posology for specific indications:
Dysmenorrhoea (painful menstruation):
Take one tablet twice daily from day 5 to day 25 of the cycle.

Endometriosis (abnormal growth of uterine tissues outside the uterus):
Take one tablet two or three times daily from day 5 to day 25 of the cycle or continuously (as prescribed by your doctor).

Dysfunctional bleeding (to stop bleeding):
Take one tablet twice daily for five to seven days.

Dysfunctional bleeding (to prevent bleeding):
Take one tablet twice daily from day 11 to day 25 of the cycle.

Amenorrhoea (cessation of menstruation):
Your doctor should prescribe an oestrogen along with Duphaston. Then take the oestrogen once daily from day 1 to day 25 of the cycle, together with one tablet of dydrogesterone twice daily from day 11 to day 25 of the cycle.

Premenstrual syndrome:
Take one tablet twice daily from day 11 to day 25 of the cycle.

Irregular cycles:
Take one tablet twice daily from day 11 to day 25 of the cycle.

Threatened abortion:
Take four tablets at once, then one tablet every eight hours until symptoms abate.

Habitual abortion:
Take one tablet twice daily until the twentieth week of pregnancy.

Infertility due to luteal (yellow body) insufficiency:
Take one tablet daily from day 14 to 25 of the cycle. Continue the treatment for at least six consecutive cycles. In addition, it is advisable to continue treatment for the first few months of pregnancy as described under 'Habitual abortion'. If you are uncertain about how long to continue the treatment, talk to your doctor.
Duphaston is not recommended for use in children below age 18 due to insufficient data on safety and efficacy.

Contraindications
Do not take Duphaston if you
- are hypersensitive (allergic) to the active substance or to any of the excipients.
- have a known or suspected progestogen dependent neoplasm.
- have undiagnosed vaginal bleeding
- are using this medicine to prevent endometrial hyperplasia (abnormal growth of the lining of the uterus), specifically if you are also taking oestrogens: See contraindications for use of oestrogens in combination with progestagens, such as dydrogesterone.

Warnings and special precautions for use
The cause of abnormal bleeding must be investigated (and found if possible) before your doctor can prescribe this medication to you to treat this problem.

Treatment with dydrogesterone has infrequently been associated with alterations in liver function, sometimes accompanied by clinical symptoms. If you suffer from acute liver disease, or have a history of liver disease your doctor will carefully evaluate your case before prescribing this medicine to you. This is particularly necessary, if your liver function tests continue to be abnormal. In cases of severe hepatic impairment your doctor will stop the treatment.

Some people experience breakthrough bleeding when treated with dydrogesterone.

Conditions which need supervision
If you have a history of, or currently suffer from porphyria (inherited or acquired disorder, preventing the proper development of haemoglobin) or depression, and/or if these conditions have been aggravated during pregnancy or previous hormone treatment, you should be closely supervised by your doctor while taking Duphaston. This is necessary because these conditions may recur or be aggravated during treatment with dydrogesterone.

Other conditions
Do not take this medicine if you suffer from any of the following rare hereditary problems: Galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

If you have been prescribed dydrogesterone for the prevention of endometrial hyperplasia (abnormal growth of the inner lining of the uterus) while using oestrogens, be sure to read the "Warnings and precautions" section in the product information leaflet of the oestrogen preparation.

If you suffer from the symptoms of postmenopausal oestrogen deficiency, your doctor can only start you on hormone replacement therapy (HRT) if your symptoms adversely affect your quality of life. Furthermore, you should see your doctor periodically (at least annually). He will reassess the advantages and disadvantages of HRT to you and continue the treatment only if the advantages continue to outweigh the disadvantages.

Medical examination / follow-up
- Your doctor will take a full medical history (including family history) before starting you on hormone replacement therapy (HRT) or when its use is to be resumed after an interruption. Your doctor will also perform a complete physical examination (including gynaecological (pelvic) and breast examination) as guided by your history and by the contra-indications and warnings described in this leaflet. During the treatment period it is highly recommended to have regular check-ups, the frequency and nature of which will be determined by your doctor according to your personal situation. Any changes in your breast must be reported to your doctor immediately. Your doctor can explain to you what types of changes are particularly important to report.
- In accordance with the current guidelines for healthy women it is important to have regular breast examinations, including mammography, performed. These should be scheduled according to your personal medical needs.

Endometrial hyperplasia (abnormal growth of the inner lining of the uterus)
- Long-term use of oestrogens without the addition of a progestagen increases the chance of endometrial hyperplasia and endometrial carcinoma (cancer) in women with an intact 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, the active ingredient in Duphaston.

Mammary cancer
- A randomised placebo-controlled study, the Women's Health Initiative Study (WHI) and epidemiological studies, including the Million Women Study (MWS) have shown that in women who have taken oestrogen, oestrogen-progestagen combinations or tibolone as hormone replacement therapy for a number of years there is a relative increased risk of breast cancer. For all HRT this increased risk occurs within a couple of years of use and increases as the treatment period continues. The risk returns to pretreatment level within a couple of years (a maximum of five) after the treatment is discontinued.
The MWS showed that the relative risk of breast cancer in women who were treated with conjugated equine oestrogens (CEE) or oestradiol (E2) was higher when a progestagen was added. This risk was independent of the dosage schedule used (sequential or continuous administration of progestagen) and the type of progestagen.

Venous thromboembolism
- Hormone replacement therapy is associated with a higher relative risk for the occurrence of a venous thromboembolism (VTE), that is deep vein thrombosis or pulmonary embolism. One randomised controlled study and epidemiological studies report a two to three times higher risk of VTE among users of HRT compared with women who do not use HRT. The chance of VTE is greater during the first year of HRT treatment than thereafter.
- General risk factors for the occurrence of VTE are:
  - o A positive personal history;
  - o A positive family history;
  - o Serious obesity (Body Mass Index greater than 30 kg/m^2);
  - o Systemic lupus erythematosus (SLE)

There is no consensus regarding the possible role of varicosis in VTE.

- If you have a previous history of repeated VTE or have thrombophilia (a blood disorder in which there is an increased tendency to form blood clots), you are at an increased risk of VTE. Hormone replacement could increase this risk even further. If you have a previous personal or clear family history of VTE or have suffered repeated spontaneous abortions, your doctor must carry out an investigation to ensure you do not have a

thrombophilic predisposition. Until a thorough evaluation of the thrombophilic factors have been carried out or anticoagulant therapy has been started, the use of HRT is contraindicated. If you are already being treated with anticoagulant therapy, your doctor must carefully assess the advantages and disadvantages of HRT treatment before starting you on it.

- The chance of VTE may be increased temporarily from long-term immobilisation, serious trauma or major surgical operation. If you are a postoperative patient, your doctors will do all that is necessary to help prevent the occurrence of a VTE after your surgery. If you are to undergo an elective surgery (in particular abdominal or orthopaedic surgery of the lower limbs), after which long-term immobilisation is anticipated, your doctor will likely stop your HRT four to six weeks before the operation. Your doctor can restart your HRT when you are fully mobile again.
- If a VTE develops after starting the therapy, you must stop taking Duphaston (your doctor will discontinue the prescription). Also, contact your doctor immediately if any potentially thromboembolic symptoms occur (for example: painful swelling of a leg, sudden pain in the chest, shortness of breath).

Coronary heart disease
- Randomised controlled studies have not provided any evidence of a favourable effect of continuous combined conjugated oestrogens and medroxyprogesterone acetate on the risk of coronary heart disease (i.e.: no positive influence on the risk of coronary heart disease seen during HRT). Two large clinical studies (WHI and HERS (Heart and Oestrogen/ progestin Replacement Study)) showed a possible increased risk of cardiovascular morbidity during the first year of use and no indications of an overall favourable effect.

Cerebrovascular accident (CVA)
- In one large randomised clinical trial (WHI study) in healthy women, as a secondary outcome, an increased risk of ischemic CVA was reported during treatment with continuous combined conjugated oestrogens with medroxyprogesterone acetate.

Interactions
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained without a prescription.

No interaction studies have been performed.

Pregnancy and lactation
Ask your doctor or pharmacist for advice before taking any medicine during pregnancy.

It is estimated that altogether roughly 35 million women have been treated with dydrogesterone. Although the number of pregnancies is difficult to estimate, as an approximation it can be assumed that foetuses were exposed to dydrogesterone in around nine million pregnancies (this high exposure in pregnancy is due to the fact that dydrogesterone has pregnancy related indications in large parts of the world). From spontaneous surveillance systems to date, there is no evidence that dydrogesterone can not be used during pregnancy. No other relevant epidemiological data on dydrogesterone are available.

However, a recent US case-controlled study investigating 502 cases with hypospadias (deformity of the penis, in which the urethra opens on the underside instead of at the end) and 1286 healthy controls suggested at least a twofold increased risk of second/third degree hypospadias among boys born by mothers who took progestogens (predominantly progesterone) shortly prior or during early pregnancy (information for the doctor: OR 2.2, 95% CI 1.0-5.0).
The causality is unclear. The underlying illness itself (which is the reason for the use of progesterone in pregnancy) may contribute to a potential risk factor for the development of hypospadias in the child. For dydrogesterone, the risk of hypospadias is unknown.

Animal studies have been conducted, however, are insufficient with respect to pregnancy, embryonal/foetal or postnatal development due to major difference in metabolism between rats and humans. The potential risk for humans is unknown.
The limited animal safety data suggest that Duphaston's active ingredient dydrogesterone has delaying effects on parturition, which is consistent with its progestogenic activity.

There is no evidence that dydrogesterone decreases fertility.

Dydrogesterone is excreted in the milk of nursing mothers. A risk to the suckling child cannot be excluded. Dydrogesterone should not be used during breast-feeding.

Effects on ability to drive and use machines
Dydrogesterone has no or negligible influence on the ability to drive and use machines.

Important information about the ingredients
Lactose monohydrate:
If you have been told by your doctor that you have an intolerance to some sugars, especially lactose, contact your doctor before taking this medicinal product.

Undesirable effects
Like all medicines, Duphaston may cause side effects. If you notice any side effects not mentioned in this leaflet, or if any of the side effects gets serious, please inform your doctor or pharmacist.

The frequencies of study related side effects are ranked according to the following:
Common: Between 1 and 10 cases in 100 treated patients
Uncommon: Less than one case in 100 treated patients
Rare: Less than one case in 1000 treated patients
Very Rare: Less than one case in 10 000 treated patients

The undesirable effects reported in clinical trials and/or in post marketing experience following dydrogesterone therapy are (according to the MedDRA organ classification system):

Blood and the lymphatic system disorders
Very rare: Haemolytic anaemia (low red blood cell count due to destruction of red blood cells)

Immune system disorders
Very rare: Hypersensitivity (allergy)

Nervous system disorders
Common: Migraines/ headache

Hepatobiliary disorders
Uncommon: Abnormal hepatic function (with jaundice, asthenia (weakness) or malaise, and abdominal pain)

Skin and subcutaneous tissue disorders
Uncommon: Allergic dermatitis (e.g. rash, pruritus (itching), urticaria (hives))
Very rare: Angioedema (sudden, non-painful accumulation of fluid under the skin)

Reproductive system and breast disorders
Common: Metrorrhagia (uterine bleeding not associated with menstruation)
Uncommon: Breast pain/ tenderness

General disorders and administration site conditions
Very rare: Oedema (swelling)

Other adverse reactions obtained from the market with unknown frequency in association with dydrogesterone treatment:

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)
- Increase in size of progestogen dependent neoplasms (e.g.meningioma; see section "Contraindications")

Psychiatric disorders
- Depressed mood

Reproductive system and breast disorders
- Breast swelling

Undesirable effects that are associated with an oestrogen-progestagen treatment (see also section "Warnings and special precautions for use"):
- Breast cancer
- Endometrial hyperplasia (abnormal growth of the inner lining of the uterus), endometrial carcinoma (cancer)
- Sex hormone dependent tumours (malignant/benign)
- Venous thrombosis
- Myocardial infarction (heart attack), cardiovascular accident.

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. Aforementioned information is also applicable for overdosing in children.

Pharmacodynamics
The following is a detailed description of how the active ingredients of Duphaston work. For further explanations please consult your doctor.

Pharmacotherapeutic group: Genitourinary 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 oestrogen induced increased risk for endometrial hyperplasia and/or carcinogenesis. It is indicated in all cases of endogenous progesterone deficiency. Dydrogesterone has no oestrogenic, no androgenic, no thermogenic, no anabolic and no corticoid activity.

Pharmacokinetics
The following is a detailed description of how the active ingredients of Duphaston are metabolized by the body. For further explanations please consult your doctor.

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 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 lack of oestrogenic 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 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.
Dydrogesterone is not excreted in urine as pregnanediol, like progesterone. Analysis of endogenous progesterone production based on pregnanediol excretion therefore remains possible.

Incompatibilities
Not applicable.

Shelf life and storage conditions
5 years.

Do not store above 30°C.

Keep the blister in the outer carton, in order to protect from moisture.

Do not use the medicine after the expiry date stated on the carton.

Keep this medicine out of the sight and reach of children.

Pack sizes
10, 14 or 20 film-coated tablets per pack (not all pack sizes may be marketed).
The blisters are made of aluminium foil and PVC film, uncoated or coated with PVDC.

Further information
Any unused product or waste material should be disposed of in accordance with local requirements.

The information in this leaflet is limited. For further information, please contact your doctor or pharmacist.

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