

Prescribing Information

DUPHASTON Film Coated Tablets

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
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 7 mm).

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

Cases where progesterone supplement is needed.

4.2 Posology and method of administration

Posology

The following dosage regimens are recommended for treatment with Duphaston. The quantities can be adjusted according to the seriousness of the disorder to be treated and the individual patients' responses to the treatment.

Regulation of the cycle

It is possible to achieve a cycle lasting 28 days by giving 1 tablet of Duphaston a day from the 11th to the 25th day of the cycle.

Endometriosis

1 to 3 tablets of Duphaston a day from the 5th to the 25th day of the cycle or for the entire cycle. Dosages of 10 mg several times a day should be spread over the day. It is recommended that treatment should start at the highest dose.

Dysmenorrhoea

1 to 2 tablets of Duphaston a day from the 5th to the 25th day of the cycle. Dosages of 10 mg several times a day should be spread over the day. It is recommended that treatment should start at the highest dose.

Infertility as a result of corpus luteum insufficiency

1 tablet of Duphaston a day from the 14th to the 25th day of the cycle.

Treatment should be continued for at least 6 consecutive cycles. It is advisable to continue this treatment for the first months of any pregnancy at dosages as indicated for habitual abortion.

Threatened abortion

Starting dose: 4 tablets of Duphaston at once followed by 1 tablet of Duphaston mg every 8 hours. Dosages of 10 mg several times a day should be spread over the day. It is recommended that treatment should start at the highest dose.

If the symptoms persist or recur during the treatment, the dose should be increased by 1 tablet of Duphaston every 8 hours.

The effective dose should be maintained for one week after symptoms have ceased; it can then be gradually reduced. If the symptoms recur, the treatment should be resumed immediately at the effective dose.

Habitual abortion

1 tablet of Duphaston a day up to the 20th week of pregnancy; the dose can then be gradually reduced. Treatment should preferably be started before conception.

If the symptoms of threatened abortion occur during treatment, treatment should be continued as described for that indication.

Dysfunctional uterine bleeding

Bleeding is stopped by 2 tablets of Duphaston a day for 5 to 7 days. The blood loss is reduced considerably within a few days. A few days after the end of this treatment, a heavy withdrawal bleed occurs and the patient should be warned about this.

Subsequent heavy bleeding can be prevented by prescribing a prophylactic dose of 1 tablet of Duphaston a day from the 11th to the 25th day of the cycle, if necessary combined with an oestrogen for 2 to 3 cycles. After this the treatment can be discontinued, in order to check that the patient has a normal cycle again.

Secondary amenorrhoea

1 or 2 tablets of Duphaston per day from the 11th to the 25th day of the cycle to give optimum secretion transformation of the endometrium, that is adequately prepared with an endogenous or exogenous oestrogen.

Pre-menstrual syndrome:

10 mg twice daily from day 11 to day 26 of the cycle.

There is no relevant use of dydrogesterone before the menarche. The safety and efficacy of dydrogesterone in adolescents aged from 12 to 18 years has not been established.

Method of administration

For oral use.

For administration of higher doses the tablets should be taken in divided doses over the day.

4.3 Contraindications

- Vaginal bleeding, where the cause has not been established.
- Presence of serious liver disorders, or serious liver disorders in the medical history until the liver function values have returned to normal.
- Contraindications for use of oestrogens in combination with progestogens such as dydrogesterone in combined therapy;
- Known hypersensitivity to dydrogesterone or any of the excipients.
- Known or suspected sex hormone dependent malignancies.

4.4 Special warnings and precautions for use

Before starting treatment with dydrogesterone because of dysfunctional uterine bleeding an organic cause should be excluded.

Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding and spotting continue to occur when treatment has already been underway for some time, or continue when treatment is discontinued, the cause of this should be ascertained, if necessary by taking an endometrial biopsy to exclude malignancy of the endometrium.

If one of the following disorders occurs during use for the first time or gets worse, stopping the treatment should be considered.

- exceptionally severe headache, migraine or symptoms that may indicate cerebral ischemia.
- marked increase in blood pressure.
- occurrence of venous thromboembolism.

In cases of habitual or threatened abortion, the viability of the foetus should be ascertained, and it is necessary to monitor during treatment whether the pregnancy is still progressing and whether the embryo is still alive.

Conditions for which monitoring is necessary:

It is known that the following rarely occurring conditions may be affected by sex hormones and may arise or get worse during pregnancy or during the use of sex hormones: cholestatic icterus, herpes gestationis, severe pruritus, otosclerosis and porphyria.

Patients with a history of depression must be carefully monitored; if severe depression recurs, treatment with dydrogesterone must be stopped.

Other conditions

Patients with rare hereditary conditions such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not use this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Data from *in vitro* studies show that dydrogesterone and its main metabolite 20 α -dihydrodydrogesterone (DHD) may be broken down by the P 450 cytochrome isoenzymes 3A4 and 2C19.

The metabolism of dydrogesterone may therefore be increased by concomitant use of substances known to induce these isoenzymes, 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 ginkgo biloba.

Ritonavir and nelfinavir are of course well-known powerful inhibitors of cytochrome enzymes but do in fact have an enzyme-inducing action if they are used concomitantly with steroid hormones.

Clinically an increase in the metabolism of dydrogesterone may lead to a reduction in effect and changes in the bleeding pattern.

In vitro studies show that dydrogesterone and DHD enzymes that metabolise CYP substances do not inhibit or induce.

4.6 Fertility, pregnancy and lactation

Pregnancy

It is estimated that over 9 million women have already been exposed to dydrogesterone during pregnancy. To date there were no indications that the use of dydrogesterone during pregnancy has a harmful effect. In the literature a study is described in which it was found that the use of some progestogens can be accompanied by an increase in the risk of hypospadias occurring. However, because this has not been clearly confirmed to date in other studies, no final conclusion can be drawn about the effect of progestogens on the occurrence of hypospadias.

Clinical trials in which a limited number of women were treated with dydrogesterone in the first stage of pregnancy did not show that the risk is increased. To date no other epidemiological data are available.

The effects that were observed during non-clinical study into embryo-foetal and postnatal development corresponded with the pharmacological profile. Unwanted effects only occurred in case of exposure that was considerably higher than the maximum exposure in humans (see section 5.3).

Dydrogesterone may be administered during pregnancy if there is a clear indication for this.

Lactation

It is not known whether dydrogesterone is excreted in breast milk. No research has been done into the excretion of dydrogesterone in breast milk. Experiences with other progestogens indicate that progestogens and their metabolites are found in small quantities in breast milk. It is not known whether there is a risk for the child. Dydrogesterone should therefore not be used while breastfeeding.

Fertility

There are no data on the effect of dydrogesterone on fertility.

4.7 Effects on ability to drive and use machines

Dydrogesterone has a slight effect on ability to drive and to use machinery.

In rare cases dydrogesterone may cause somnolence and/or dizziness, in particular during the first couple of hours after taking it. Caution is therefore advised when driving and operating machinery.

4.8 Undesirable effects

The adverse effects of this product most commonly reported in patients who were treated with dydrogesterone during clinical trials into indications without the use of oestrogen were metrorrhagia, painful/ sensitive breasts and migraine/headache.

The following adverse effects, with the frequencies indicated, were observed during clinical trials with dydrogesterone (n=3,483) for indications without the use of oestrogen, and were reported spontaneously:

Organ class according to MedDRA database	Common ≥1:100, <1:10	Uncommon ≥1:1,000, <1:100	Rare ≥1:10,000, <1:1,000
Neoplasms, benign, malignant and non-specified (including cysts and polyps)			Growth of progestogen-dependent neoplasms (e.g. meningioma)*
Blood and lymphatic system disorders			Haemolytic anaemia*
Psychiatric disorders		Depression	
Immune system disorders			Hypersensitivity
Nervous system disorders	Migraine/headache	Dizziness	Somnolence
Gastrointestinal disorders	Nausea	Vomiting	
Hepatobiliary disorders		Disturbed liver function (with icterus, asthenia or malaise, and abdominal pain)	
Skin and subcutaneous tissue disorders		Allergic dermatitis (e.g. rash, pruritus, urticaria)	Angiooedema*
Reproductive system and breast disorders	Disturbed menstruation (including metrorrhagia, menorrhagia, oligo-/amenorrhoea, dysmenorrhoea and irregular menstruation) Painful/ sensitive breasts		Swelling of the breasts
General disorders and administration site conditions			Oedema
Investigations		Weight gain	

* Adverse effects reported spontaneously but not observed during clinical trials are classified as “rare” in view of the fact that the upper limit of the 95% confidence interval of the estimated frequency is not higher than $3/x$, where $x=3,483$ (the total number of patients in the clinical trials).

Adverse effects that may occur during treatment with oestrogen-progestogen (see also the section “Warnings and precautions for use” and the product information for the oestrogen preparation):

- Breast cancer, endometrial hyperplasia, endometrial carcinoma, ovarian cancer
- Venous thromboembolism
- Myocardial infarction, coronary heart disease, ischemic CVA

4.9 Overdose

Symptoms

Dydrogesterone is a substance with very low toxicity. Nausea, vomiting, lethargy and dizziness are symptoms which may theoretically occur in the event of an overdose. There are no known cases in which an overdose of dydrogesterone led to harmful effects.

Treatment

Specific treatment is clearly not necessary. In case of overdose symptomatic treatment may be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic category: urogenital system and sex hormones, ATC code: G03DB01

Dydrogesterone is a synthetic progesterone with an oral biological availability that causes a secretory phase of the endometrium in a uterus prepared by oestrogen. It gives protection against the increased risk of endometrial hyperplasia and/or endometrial carcinoma that is induced by oestrogens. Dydrogeserone has no oestrogenic, androgenic, anabolic and corticoid properties.

Dydrogesterone does not suppress ovulation. As a result, conception remains possible if dydrogesterone is used by women of child-bearing age.

In postmenopausal women with a uterus, oestrogen replacement leads to an increase in the risk of endometrial hyperplasia and endometrial carcinoma. The addition of a progestogen prevents this additional risk.

5.2 Pharmacokinetic properties

Absorption:

After oral administration dydrogesterone is rapidly absorbed with a T_{max} of between 0.5 and 2.5 hours. The absolute biological availability of dydrogesterone (20 mg oral dose versus 7.8 mg intravenous infusion) is 28%.

The following tables gives the pharmacokinetic parameters of dydrogesterone (D) and 20 α -dihydrodydrogesterone (DHD) after administration of a single dose 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 distribution volume is around 1400 l. More than 90% of dydrogesterone and DHD are bound to plasma-proteins.

Metabolism:

After oral administration dydrogesterone is quickly metabolised to DHD. The plasma levels of the main active metabolite DHD show a peak around 1.5 hours after administering the dose. The plasma levels of DHD are substantially higher than the related medicinal product. The AUC and C_{max} ratios of DHD and dydrogesterone are of the order of magnitude of respectively 40 and 25. The mean terminal half-life of dydrogesterone and DHD varies from respectively 5 to 7 and 14 to 17 hours. A common characteristic of all characterised

metabolites is the retention of the 4,6-diene-2-one configuration of the original product and the absence of 17 α hydroxylation. This explains the absence of oestrogenic and androgenic effects of dydrogesterone.

Elimination

After oral administration of labelled dydrogesterone on average 63% of the dose is excreted in the urine. The total plasma clearance is 6.4 l/minute. Within 72 hours the excretion is complete, DHD is present in the urine mainly as the conjugated glucuronic acid.

Dependence of dose and time

The pharmacokinetics of single and multiple doses are linear in the oral dosage range from 2.5 to 10 mg. Comparison of the kinetics of single and multiple doses shows that the pharmacokinetics of dydrogesterone and DHD do not change as a result of repeated dosing. Steady state is reached after 3 days of treatment.

5.3 Preclinical safety data

Non-clinical data obtained during conventional investigation into the toxicity of single and repeated doses, genotoxicity and the carcinogenic potential do not show any special risks for humans.

Research into the toxic effects on the reproduction of rats shows for high doses (>80 times the human exposure) an increased incidence of erect nipples (during days 11-19 of the lactation period) and of hypospadias in male rats. The clinical relevance of these observations is not known.

The limited data on safety in animals indicate that dydrogesterone has an extending effect on delivery, which corresponds with the progestogenic action.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, methylhydroxypropylcellulose, maize starch, colloidal anhydrous silica, magnesium stearate, Opadry Y-1-7000

6.2 Cases of incompatibility

None

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store in a dry place, below 30°C.

6.5 Nature and contents of container

20 Tablets blister strips of aluminium foil (0.02mm) and PVC film (0.2mm).

6.6 Special precautions for disposal

All unused medicinal product or waste material must be disposed of in accordance with local regulations.

7. MANUFACTURER

Abbott Healthcare Products B.V., Netherlands

8. MARKETING AUTHORISATION HOLDER

Abbott Medical Laboratories Ltd.,
Kiryat Atidim, POB 58099, Tel Aviv, 61580.

9. MARKETING AUTHORISATION NUMBER

129-45-30880-00.

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