DUPHASTON
Film Coated Tablets

1. NAME OF THE MEDICINAL PRODUCT

Duphaston

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg dydrogesterone.
Excipient with known effect: 111.1 mg lactose monohydrate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

A round, biconvex, white film-coated tablet, (with a diameter of 7 mm) with a score line, with the inscription '155' on both sides of the score line.

The score line is only to make the tablet easier to break so that it is easier to swallow; it is not intended for dividing it 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 11^{th} to the 25^{th} day of the cycle.

Endometriosis
1 to 3 tablets of Duphaston a day from the 5^{th} to the 25^{th} 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 to start treatment with the highest dosage.

Dysmenorrhoea
1 to 2 tablets of Duphaston a day from the 5^{th} to the 25^{th} day of the cycle. Dosages of 10 mg several times a day should be spread over the day. It is recommended to start the treatment with the highest dosage.

Infertility as a result of corpus luteum insufficiency
1 tablet of Duphaston a day from the 14^{th} to the 25^{th} 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.

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

Threatened abortion
Starting dose: 4 tablets of Duphaston at once followed by 1 tablet of Duphaston 10 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 prohylactic 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 evenly distributed over the day.

4.3 Contraindications

- Vaginal bleeding, where the cause has not been established.
- Treatment for luteal support as part of an Assisted Reproductive Technology (ART) treatment should be discontinued upon diagnosis of abortion or miscarriage.
- 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.
- Hypersensitivity to the active ingredient or to any of the excipients listed in Section 6.1.
- Known or suspected sex hormone dependent malignancies.

4.4 Special warnings and precautions for use

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

Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeeding 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.

Excipients
This medicinal product contains lactose monohydrate.
Patients with rare hereditary conditions, such as galactose intolerance, Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro data that the main active metabolite 20α-dihydrodydrogesterone (DHD) and to less extent also dydrogesterone are primarlily metabolized by CYP3A4.
Substances that increase the clearance of progestogens (less efficacy due to enzyme induction) are for example: barbiturates, phenytoin, carbamazepine, primidone, rifampicin and HIV medication like ritonavir, neviparine and efavirenz, and possibly also products containing the herb St. John's Worth (hypericum perforatum).
An increase in the clearance of dydrogesterone may lead to a clinical decrease of effect and changes in the bleeding pattern.

Substances with variable effects on the clearance of progestogens:
Many combinations of HIV protease inhibitors and non-nucleoside reverse-transcriptase inhibitors, including combinations with HCV inhibitors could, if concomitantly administered with progestogens, raise or lower the plasma concentrations of the progestogen. In some cases the net effect of these changes could be clinically relevant.

For this reason the product information of HIV/HCV medicines should be consulted, if they are administered concomitantly, to determine potential interactions and any associated recommendations.

Substances that decrease clearance of progestogens (enzyme inhibitors):
The clinical relevance of possible interactions with enzyme inhibitors is unknown. Concomitant use of strong CYP3A4 inhibitors may raise the plasma concentrations of progestogens.

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 hypospadia 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 hypospadia.

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 afer 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 drydrogesterone 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 clincal 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).

<u>LOTUS I study for luteal support as part of an Assisted Reproductive Technology (ART)</u>

treatment (see section 5.1):

The most frequently reported events are vaginal hemorrhage, nausea, procedural pain, headache, abdominal pain and biochemical pregnancy.

The only related treatment emergent adverse event (TEAE) reported in ≥ 2% of subjects in either treatment group is vaginal hemorrhage.

Adverse effects that may occur during treatment with oestrogen-progestogen (see also the section 4.4 and the product information for the oestrogen formulation):

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il.

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

Mechanism of action
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 additonal risk.

Clinical efficacy and safety

Luteal support as part of an Assisted Reproductive Technology (ART) treatment:

A Double-Blind, Double-Dummy, Randomized, Two-arm, Multicentre 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)

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

In the studied patient population, pregnancy rates at 12 weeks' gestation (week 10) were 37.6% and 33.1% in the dydrogesterone and micronized progesterone groups, respectively. The difference in the pregnancy rate between the two groups was 4.7 (95% CI, -1.2; 10.6).

Within the safety sample of 1,029 subjects with at least one dose of study medication administered, the incidence of the most frequently reported TEAEs was similar between the two treatment groups.

Due to the nature of the indication and the studied patient population, a number of early abortions and miscarriages can be expected. Especially until 12 weeks' gestation (pregnancy week 10), the expected pregnancy rate is about 35%.

The safety profile observed in this study is in line with the profile as known for dydrogesterone for the treatment target population and indication.

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 20α-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 dydrgesterone is metabolized quickly to DHD. In vitro data show that the main route of metabolism, the one that generates DHD, is catalyzed in human cytosol by aldo-keto reductase 1C (AKR 1C). Next to this cystolic metabolism, other metabolic routes by cytochrome P450 iso enzymes (CYPs) exist, this is nearly exclusively CYP 3A4, in which less important metabolites are formed. The concentration of the main active metabolite DHD shows a peak concentration approximately 1.5 hours after administration. The plasma concentrations of DHD are substantially higher than the related drug. The AUC and Cmax ratios of DHD and dydrogesterone are approximately 40 and 25. The mean terminal half-life

of dydrogesterone and DHD varies from 5-7 and 14-17 hours respectively. A common feature of all characterized metabolites is the maintenance of the 4,6-diene-3-on configuration of the initial drug and the missing 17a-hydroxylation. This clarifies the lack of estrogen and androgen 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 toxixcity 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 hypospadia 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

Composition of the tablet:
Lactose monohydrate, methylhydroxypropylcellulose, maize starch, colloidal anhydrous silica, magnesium stearate

Composition of the coating:
Opadry Y-1-7000 [Hypromellose, Macrogol 400, Titanium dioxide (E171)]

6.2 Cases of incompatibility

None

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

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

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

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

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