Prescribing Information

DUPHASTON
Tablets

Name of the medicinal product
Duphaston 10mg film-coated tablets

Qualitative and Quantitative Composition
Dydrogesterone film-coated tablets contain 10 mg dydrogesterone per tablet.

Pharmaceutical Form
A round, biconvex, scored, white coloured film-coated tablet, one side bearing the inscription ‘8’, the other side bearing the inscription ‘155’ on either side of the break mark.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Indications

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysmenorrhoea</td>
<td>10 mg twice daily from day 5 to day 25 of the cycle.</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>10 mg two or three times daily from day 5 to day 25 of the cycle or continuously.</td>
</tr>
<tr>
<td>Dysfunctional bleeding (to arrest bleeding)</td>
<td>10 mg twice daily for five to seven days.</td>
</tr>
<tr>
<td>Dysfunctional bleeding (to prevent bleeding)</td>
<td>10 mg twice daily from day 11 to day 25 of the cycle.</td>
</tr>
</tbody>
</table>
Amenorrhoea : an oestrogen once daily from day 1 to day 25 of the cycle, together with 10 mg dydrogesterone twice daily from day 11 to day 25 of the cycle.

Pre-menstrual syndrome : 10 mg twice daily from day 11 to day 25 of the cycle.

Irregular cycles : 10 mg twice daily from day 11 to day 25 of the cycle.

Threatened abortion : 40 mg at once, then 10 mg every eight hours until symptoms remit.

Habitual abortion : 10 mg twice daily until the twentieth week of pregnancy.

Infertility due to luteal Insufficiency : 10 mg daily from day 14 to 25 of the cycle. Treatment should be maintained for at least six consecutive cycles. It is advisable to continue treatment for the first few months of pregnancy as described under 'Habitual abortion'.

Duphaston is not recommended for use in children below age 18 due to insufficient data on safety and efficacy.

**Contraindications**

Hypersensitivity to the active substance or to any of the excipients.

Known or suspected progestogen dependent neoplasms.

Undiagnosed vaginal bleeding

**Special warnings and precautions for use**

Before initiating treatment with dydrogesterone for abnormal bleeding, the etiology for the bleeding should be clarified.

Treatment with dydrogesterone has infrequently been associated with alterations in liver function, sometimes accompanied by clinical symptoms. Thus, dydrogesterone should be used with caution in patients with acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal. In cases of severe hepatic impairment treatment should be discontinued.

Breakthrough bleeding may occur in a few patients.

**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 Trademark, in particular:
1. Porphyria
2. Depression

Other conditions

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Pregnancy and lactation

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 in utero foetuses were exposed to dydrogesterone in around 9 million pregnancies\(^1\). 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-control study investigating 502 cases with hypospadias and 1286 healthy controls suggested at least a 2-fold increased risk of second/third degree hypospadias among boys born by mothers who took progestogens (predominantly progesterone) shortly prior or during early pregnancy (OR 2.2, 95% CI 1.0-5.0). The causality is unclear as the indication for progesterone in pregnancy may be potential risk factors for hypospadias. For dydrogesterone, the risk of hypospadias is unknown.

Animal studies have been conducted, however, are insufficient with respect to pregnancy, embryonal/fetal, or postnatal development due to major difference in metabolism between rats and humans (for details see section "preclinical safety data"). The potential risk for humans is unknown.

Limited animal safety data suggest that dydrogesterone has delaying effects on partuition, which is consistent with its progestogenic activity.

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. There is no evidence that dydrogesterone decreases fertility at therapeutic dose.

Effects on ability to drive and use machines

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

---

\(^1\) This high exposure in pregnancy is due to the fact that dydrogesterone has pregnancy related indications in large parts of the world.
Undesirable effects

The undesirable effects reported in clinical trials and/or in post marketing experience following dydrogesterone therapy are:

<table>
<thead>
<tr>
<th>MedDRA system organ class</th>
<th>Common &gt;1/100, &lt;1/10</th>
<th>Uncommon &gt;1/1,000, &lt;1/100</th>
<th>Rare &gt;1/10,000, &lt;1/1,000</th>
<th>Very rare &lt;1/10,000 incl. isolated reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
<td>Haemolytic anaemia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Migraines/ headache</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td>hepatic function abnormal (with jaundice, asthenia or malaise, and abdominal pain)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>Dermatitis allergic (e.g. rash, pruritus, urticaria)</td>
<td></td>
<td>Angioedema</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Metrorrhagia</td>
<td>Breast pain/ tenderness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td>Oedema</td>
</tr>
</tbody>
</table>

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 4.3).

Psychiatric disorders
Depressed mood

Reproductive system and breast disorders
Breast swelling
**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). 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. Aforementioned information is also applicable for overdosing in children.

**Pharmacological properties**

**Pharmacodynamic properties**
Pharmaco-therapeutic group: Genito Urinary system and sex hormones, ATC code: G03DB01

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.

**Pharmacokinetic properties**
After oral administration of labeled 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 4,6diene-3-one configuration of 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 substantially higher as compared to the parent drug. The AUC and C<sub>max</sub> ratios of DHD to dydrogesterone are in the order of 40 and 25, respectively.

Dydrogesterone is rapidly absorbed. The T<sub>max</sub> 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.

**Preclinical safety data**
Receptor binding studies and functional activity studies revealed antiandrogenic potency of progesterone, dydrogesterone and its metabolite dihydrodydrogesterone (DHD). The antiandrogenic potency of dydrogesterone and its metabolite DHD is probably noticeably weaker than that of progesterone. With regard to antiandrogenic effects mediated by inhibition of 5α-reductase type II, an important enzyme for differentiation of the male
external genitalia, progesterone is as potent as the synthetic enzyme inhibitor finasteride, whereas dydrogesterone and DHD are inactive. The overall potential to act as antiandrogenic endocrine disruptors may be rated as highest for Progesterone, lower for Dydrogesterone and lowest for DHD.

Embryofetal developmental studies were conducted in rats and rabbits using high dosages of dydrogesterone. No structural adverse effects were recorded in the foetal offspring. In a subsequent peripostnatal developmental study pregnant rats were treated with similar dosages of dydrogesterone during the period of gestation, and pups were raised. There were occasions of hypospadias in the male offspring but only at the highest dose. The next lower dose of dydrogesterone showed a sufficient safety margin in rat plasma exposure (>80 fold) compared to the estimated exposure at the maximum human daily dose of 60 mg. However, due to major species differences in metabolism between rats and humans, no adequate margin of exposure could be determined for the main human metabolite dihydrodydrogesterone.

Limited animal safety data suggest that dydrogesterone has delaying effects on parturition, which is consistent with its progestogenic activity. Dydrogesterone has been used in several animal models and has been proven to be an entity with low toxicity, not having mutagenic or carcinogenic properties.

**Pharmaceutical particulars**

**List of excipients**

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

**Incompatibilities**

None known

**Shelf-life**

5 years.

**Special precautions for storage**

Do not store above 30°C. Keep in a dry place.

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

**Nature and contents of container**

- Blister strips of aluminium foil and PVC film, coated with PVDC of 20 tablets

**Special precautions for disposal**

Any unused product or waste material should be disposed of in accordance with local requirements.
Manufacturer: Solvay Pharmaceuticals

Importer: Perrigo Israel Agencies Ltd.

22.2.2010

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved by it in February 2010.