Dydrogesterone is a progestogen, which is a type of hormone that plays a role in the female reproductive system. It is used to treat various conditions, such as dysmenorrhea, endometriosis, and dysfunctional uterine bleeding. In addition, it is used to prevent or treat threatened abortion, infertility due to luteal insufficiency, habitual abortion, and secondary amenorrhea. It is also used in hormone replacement therapy to manage symptoms of menopause.

**Pharmacology**

Dydrogesterone is an orally-active progestogen which produces a progestational effect in the endometrium without exogenous estrogen. It is metabolized in the liver and excreted primarily in the urine as the glucuronic acid conjugate of its metabolite, 4,6-diene-3-one progestosterone (DHD) and 2α-hydroxy-DHD. The metabolites are not excreted in urine as pregnanediol, like progesterone. Analysis of 4,6-diene-3-one is required for the diagnosis of endometrial hyperplasia and/or endometrial cancer. It is indicated in all cases of abnormal endometrial production of estrogen. Hydrogesterone has no estrogenic, no androgenic, no thermogenic, no analgesic and no anticoagulant activity.

**Pharmacokinetics**

Dydrogesterone is absorbed from the gastrointestinal tract and distributed to all body tissues. It is extensively metabolized in the liver and excreted primarily in the urine as the glucuronic acid conjugate of its metabolite, 4,6-diene-3-one progestosterone (DHD). Approximately 5% of the oral dose is excreted unchanged in the urine. DHD is metabolized in the urine, and is also present in the urine predominantly as the glucuronic acid conjugate. The metabolites of hydrogesterone are not excreted in urine as pregnanediol, like progesterone. Analysis of 4,6-diene-3-one is required for the diagnosis of endometrial hyperplasia and/or endometrial cancer.

**DOSAGE AND ADMINISTRATION**

- **Endometriosis**: 10 or 20 mg dydrogesterone per day from day 5 to day 25 of the menstrual cycle.
- **Secondary amenorrhea**: 10 or 20 mg dydrogesterone per day for 10 to 12 days starting at the third day of the menstrual cycle. The dosage should be tapered over 2 - 3 weeks.
- **Treatment of threatened abortion**: 20 or 30 mg dydrogesterone per day from day 5 to day 15 of the menstrual cycle. The dosage should be tapered over 2 - 3 weeks.
- **Breast cancer**: 20 mg dydrogesterone per day from day 5 to day 25 of the menstrual cycle. The dosage should be tapered over 2 - 3 weeks.
- **Secondary amenorrhea**: 10 or 20 mg dydrogesterone per day for 10 to 12 days starting at the third day of the menstrual cycle. The dosage should be tapered over 2 - 3 weeks.
- **Threatened abortion**: 20 or 30 mg dydrogesterone per day from day 5 to day 25 of the menstrual cycle. The dosage should be tapered over 2 - 3 weeks.
- **Breast cancer**: 20 mg dydrogesterone per day from day 5 to day 25 of the menstrual cycle. The dosage should be tapered over 2 - 3 weeks.

**Pharmacodynamics**

Dydrogesterone has no oestrogenic, no androgenic, no progestagenic effect. It is indicated in all cases of abnormal endometrial production of estrogen. Hydrogesterone has no estrogenic, no androgenic, no thermogenic, no analgesic and no anticoagulant activity.

**Side Effects**

Common side effects include breast tenderness, acne, and weight gain. Rare side effects may include fluid retention, bloating, and increased risk of thrombosis. Women should be advised to report any changes in their breasts 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 estrogens 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 estrogen therapy for at least 12 days per cycle with a progestagen, such as dydrogesterone.**

**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.
and from spontaneous reporting:

Dydrogesterone (n=3483) in indications without estrogen treatment

frequencies indicated below during clinical trials using

estrogen treatment are migraines/headache, nausea, menstrual

disorders (frequency <1%), rare (frequency <0.1%), very rare (frequency

less than 1/10,000), treatment-emergent (frequency unknown).

Therefore, care should be taken when driving or using machines.

infrequently, dydrogesterone may cause mild somnolence

and/or dizziness, especially within the first few hours after intake.

Effects on ability to drive and use machines

should not be used during the lactation period.

whether the metabolites pass to mother's milk in small quantities. Whether

Experience with other progestogens indicates that progestogens and

and/or dexamethasone. Whether dydrogesterone and its metabolites

at clinically relevant concentrations.

Dydrogesterone was well tolerated after oral dosing (maximum daily

dose: 20 mg). Limited data are available with regard to overdose in humans.

OVERDOSAGE

Limited data are available with regard to overdose in humans.

Dydrogesterone is well tolerated after oral dosing (maximum daily
dose: 20 mg). No reports of effects from overdose have been recorded. If
a large overdose is discovered within two or three hours and there are
depressed metabolic rate, which could be increased by concomitant
administration of systemic cytochrome P450 enzymes.

In vitro studies have shown that dydrogesterone does not induce CYP
enzymes such as CYP3A4, CYP2C9, CYP2C19, CYP2D6 or CYP2C8.

CONTRAINDICATIONS

Patients with rare hereditary problems of galactose intolerance, the

Laplace lactase deficiency or fructose intolerance may not take this medicine.

INTERACTIONS

The relative risk of CAD during use of combined estrogen-progestogen 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.

The relative risk does not change with age or time since menopause.

However, as the baseline risk of stroke is strongly dependent on age, the overall risk of stroke in women who
use HRT will increase with age.

Exempts:

This medicinal product contains Lactose monohydrate.

Patients with rare hereditary problems of galactose intolerance, the

Laplace lactase deficiency or fructose intolerance may not take this medicine.

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 hypoglycemia. However due to confounding factors during pregnancy, no definitive conclusion can be
drawn regarding the contribution of progestogens to hypoglycemia.

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 forthwith 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 ≥0.1/10), very rare (frequency ≤0.1/10), 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:

<table>
<thead>
<tr>
<th>Adverse react.</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>≥1/10</td>
<td>0.1/10</td>
<td>&lt;0.01/10</td>
</tr>
<tr>
<td>Nausea</td>
<td>≥1/10</td>
<td>0.1/10</td>
<td>&lt;0.01/10</td>
</tr>
<tr>
<td>Migraines</td>
<td>≥1/10</td>
<td>0.1/10</td>
<td>&lt;0.01/10</td>
</tr>
<tr>
<td>Nervousness</td>
<td>≥1/10</td>
<td>0.1/10</td>
<td>&lt;0.01/10</td>
</tr>
<tr>
<td>Abnormal uterine bleeding</td>
<td>≥1/10</td>
<td>0.1/10</td>
<td>&lt;0.01/10</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>≥1/10</td>
<td>0.1/10</td>
<td>&lt;0.01/10</td>
</tr>
<tr>
<td>Dysfunctional uterine bleeding</td>
<td>≥1/10</td>
<td>0.1/10</td>
<td>&lt;0.01/10</td>
</tr>
</tbody>
</table>

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.

MedDRA system organ class

COMMON

Common

Uncommon

Rare

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic and nutritional disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental and behavioral disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstetrics and gynecology disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ophthalmological disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and appendage disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urogenital disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

These systems and sub-systems are used to organize MedDRA system organ classes in the MedDRA dictionary.

The data are reported in order of frequency. Data are updated according to the MedDRA dictionary version 3.0.

SOLID 1000298265

V4.0 15-Jan-2016

01-218R4