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SCHEDULING STATUS S4

PROPRIETARY NAME (AND DOSAGE FORM)

DUPHASTON 10 mg TABLETS

Film-coated tablets

COMPOSITION

1 tablet contains dydrogesterone (9beta,10alpha-pregna-4,6-diene-3,20-dione) 10 mg.

PHARMACOLOGICAL CLASSIFICATION

A.21.8.2 Progesterones without estrogens.

PHARMACOLOGICAL ACTION

Dydrogesterone is an orally active progestogen which acts directly on the uterus, producing a complete secretory endometrium in an oestrogen-primed uterus. At therapeutic levels, dydrogesterone has no contraceptive effect as it does not inhibit or interfere with ovulation or the corpus luteum.

Dydrogesterone is non-androgenic, non-oestrogenic, non-corticoid, non-anabolic and is not excreted as pregnanediol.

Pharmacokinetics:

After oral administration of labelled dydrogesterone on average 63% of the dose is excreted into the urine. Within 72 hours excretion is complete. The main metabolite of dydrogesterone is 20α-dihydrodydrogesterone (DHD) and is present in the urine predominantly as the glucuronic acid conjugate.

After oral administration of dydrogesterone, plasma concentrations of DHD are substantially higher as compared to the parent substance. 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 are about 1.5 hours.

Mean terminal half lives of dydrogesterone and DHD vary between 5 to 7 and 14 to 17 hours, respectively.

INDICATIONS

Irregular duration of cycles and irregular occurrence and duration of periods caused by progesterone deficiency.

Combined with an oestrogenic substance, Duphaston can be applied in secondary amenorrhoea, dysfunctional uterine bleeding and post-menopausal complaints where endogenous progesterone deficiency is implicated.

CONTRA-INDICATIONS

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Duphaston should not be given to patients with undiagnosed vaginal bleeding nor to those with a history of thromboembolic disorders.

Known or suspected progestogen dependent neoplasms.

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

If used to prevent endometrial hyperplasia (in women using estrogens): Contraindications for use of oestrogens in combination with progestogens, such as dydrogesterone.

WARNINGS

See Special precautions.

INTERACTIONS:

No interaction studies have been performed.

PREGNANCY AND LACTATION:

Safety of Duphaston in pregnancy has not been established.

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 Duphaston the risk of hypospadias is unknown.

Dydrogesterone is excreted in the milk of breastfeeding mothers. Duphaston should not be used during breastfeeding.

DOSAGE AND DIRECTIONS FOR USE

In general

The dosage schemes below are meant as general recommendations. For optimal therapeutic effect, the dosages are to be adapted to the nature and severity of the disorder. In irregular cycles due to endogenous progesterone deficiency Duphaston 10 mg is recommended especially in irregular cycles due to shortened luteal phase (i.e. pre-menopause). Treatment should be repeated for several cycles.

In secondary amenorrhoea

Administration of Duphaston in combination with an oestrogen is usually recommended as in these conditions endogenous progesterone deficiency is nearly always accompanied by oestrogen deficiency. 0,05 mg ethinylestradiol is administered each day from the 1st to the 25th day of the cycle, and Duphaston is added twice daily from the 11th to the 25th day. Five days after the subsequent withdrawal bleeding, the same is repeated to imitate a natural cycle.

In dysfunctional uterine bleeding

The symptomatic treatment is aimed at stopping the bleeding and including a subsequent withdrawal bleeding.

- To stop bleeding:

  Duphaston 10 mg together with 0,10 mg ethinylestradiol twice daily for 5 to 7 days.

- To prevent heavy bleedings:

  Duphaston 10 mg twice daily from day 11 to day 25 of the cycle, if necessary, combined with an oestrogen during the first half of the cycle.

In post-menopausal complaints

If for the symptomatic treatment of post-menopausal complaints oestrogens are used (hormone replacement therapy - HRT), Duphaston 10 mg is used to counteract the effects of unopposed oestrogens on the endometrium. A subsequent withdrawal bleeding is induced.

- If on continuous oestrogen therapy:

  Duphaston 10 mg twice daily during the first 12 to 14 days of each calendar month.

- If on cyclic oestrogen therapy:

  Duphaston 10 mg twice daily during the last 12 to 14 days of the treatment.

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

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side effects:

The most commonly reported side-effects of patients treated with dydrogesterone in clinical trials of indications without oestrogen treatment are metrorrhagia, breast pain/tenderness, and migraines/headache.

The following undesirable effects have been observed with the below indicated frequencies during clinical trials using Duphaston (n=3324) in indications without oestrogen treatment.

MedDRA system organ class	**Common ≥1/100, <1/10**	**Uncommon ≥1/1,000, <1/100**	**Rare ≥1/10,000, <1/1,000**
Immune system disorders			Hypersensitivity
Psychiatric disorders		Depressed mood	
Nervous system disorders	Migraines/ headache		
Hepatobiliary disorders		Abnormal hepatic function (with Jaundice, Asthenia or Malaise, and Abdominal pain)	

MedDRA system organ class	**Common ≥1/100, <1/10**	**Uncommon ≥1/1,000, <1/100**	**Rare ≥1/10,000, <1/1,000**
Skin and subcutaneous tissue disorders		Allergic skin reactions (e.g. rash, pruritus, urticaria)	
Reproductive system and breast disorders	Metrorrhagia Breast pain/tenderness		Breast swelling
General disorders and administration site conditions		Oedema	
Investigations		Increased weight	

Other adverse reactions obtained from post marketing with unknown frequency in association with dydrogesterone treatment:

- Benign, malignant and unspecified neoplasms (including cysts and polyps);
- Increase in size of progestogen dependent neoplasms (e.g. meningioma), (see CONTRA-INDICATIONS);
- Blood and lymphatic system disorders;
- Haemolytic anaemia;
- Skin and subcutaneous tissue disorders;

- Angioedema;
- Breast swelling.

Undesirable effects that are associated with an oestrogen-progestogen treatment (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE):

- Breast cancer;
- Endometrial hyperplasia, endometrial carcinoma;
- Sex hormone dependent tumours (malignant/benign);
- Venous thrombosis;
- Myocardial infarction, cardiovascular accident.

Special precautions:

Duphaston should be used with caution in patients with cardiovascular, renal or hepatic impairment, diabetes mellitus, asthma, epilepsy and migraine. It should be used with care in persons with a history of mental depression.

Before initiating treatment with Duphaston for abnormal bleeding, the aetiology for the bleeding should be clarified.

Treatment with Duphaston has been associated with alterations in liver function, sometimes accompanied by clinical symptoms. Thus, Duphaston 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. This can, however, be prevented by increasing the dosage.

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 Duphaston, 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.

Warnings and precautions when using Duphaston in the indication “To prevent endometrial hyperplasia in women using oestrogens”:
NB: See also the warnings in the product information of the oestrogen preparation.

For the treatment of symptoms of oestrogen deficiency in post-menopausal women treatment with hormone replacement therapy (HRT) must only be started if these symptoms adversely affect the quality of life. Periodically, at least annually, a careful assessment of the advantages and disadvantages of HRT must be carried out and the treatment must only be continued if the advantages outweigh the disadvantages.

Medical examination / follow-up:

- Before starting hormone replacement therapy (HRT) or when its use is resumed after an interruption a full medical history (including family history) must be taken. Physical examination (including gynaecological and breast examination) must be carried out as guided by the history, the contra-indications and the warnings. During the treatment period regular check-ups are recommended, the frequency and nature of which are adapted to the individual. Women must be told what changes in their breasts they must report to their doctor.
- Regular examination of the breasts, including a mammography, must be carried out in accordance with the current guidelines for healthy women, taking into account here the medical need of the individual woman.

Endometrial hyperplasia:

- Long-term use of oestrogens without addition of progestagens increases the chance of endometrial hyperplasia and endometrial carcinoma in women with a 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.

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-progestogen 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 within a couple of years (a maximum of 5) after the treatment is discontinued to the level before the treatment.

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 progestogen was added. This risk was independent of the dosage schedule used (sequential or continuous administration of progestogen) and the type of progestogen.

If any progestogen dependent neoplasms e.g. meningioma have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patients should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Duphaston.

Venous thrombo-embolism:

- Hormone replacement therapy is associated with a higher relative risk of the occurrence of a venous thromboembolism (VTE), that is deep vein thrombosis or pulmonary embolism. One randomised controlled study and epidemiological studies report 2-3 times higher risk of VTE among users of HRT compared with women who do not use HRT. The chance of this is greater during the first year of HRT treatment than thereafter.

- General risk factors for the occurrence of VTE are:
  - A positive personal history;
  - A positive family history;
  - Serious obesity (Body Mass Index > 30 kg/m^2);
  - Systemic lupus erythematosus (SLE).

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

- Patients with a previous history of repeated VTE or known thrombophilia have an increased chance of VTE. Hormone replacement could increase this risk even further. In the presence of a previous personal or clear family history of VTE or repeated spontaneous abortion an investigation must first be carried out to exclude 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 in these patients is contra-indicated. In women who are already being treated with anticoagulant therapy, a careful assessment of the advantages and disadvantages of the treatment must be made.

- The chance of VTE may have increased temporarily during long-term immobilisation, serious trauma or major surgical operation. As in all post-operative patients careful attention must be paid to prophylactic measures to prevent VTE after surgery. If after elective surgery (in particular abdominal or orthopaedic surgery of the lower limbs) long-term immobilisation is anticipated, consideration must be given to interrupting the

HRT 4-6 weeks before the operation and only resuming it when the woman is fully mobilized again.

- If a VTE develops after starting the therapy, the administration of the medication must be discontinued. Patients must be informed that they should contact their doctor immediately if potential thrombo-embolic 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. Two large clinical studies (WHI and HERS (Heart and Estrogen/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 ischaemic CVA was reported during treatment with continuous combined conjugated oestrogens with medroxyprogesterone acetate.

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KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Limited data are available with regard to overdose in humans. There are no specific antidotes and treatment should be symptomatic.

IDENTIFICATION

A round, biconvex, scored, white film-coated tablet, one side with inscription '155' on either side of the score.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

PRESENTATION

Available in packs of 30 tablets.

STORAGE INSTRUCTIONS

Store in a dry, dark place at temperatures not exceeding 25°C.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

S/21.8.2/165

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Abbott Laboratories S.A. (Pty) Ltd

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The Package Insert has been checked and is free of typographical and grammatical errors Initials:____

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