

Dytinum

(Dydrogesterone)

ڈائٹینم
(ڈائیڈرو جیسٹرون)

COMPOSITION:

Each Film Coated Tablet Contains:

Dydrogesterone.... 10mg

Product Complies B.P. Specs

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic 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 20 α -dihydrogesterone (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 17 α -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 Cmax 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 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 5 α 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 disruptors may be rated as highest for progesterone, lower for dydrogesterone and lowest for DHD.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal / foetal or postnatal development.

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.

INDICATIONS:

Adjunct to oestrogen replacement therapy

Including combination with cyclical oestrogen therapy

Progesterone deficiencies

Treatment of progesterone deficiencies such as:

- Treatment of dysmenorrhoea
- Treatment of endometriosis
- Treatment of secondary amenorrhoea
- 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

POSODOLOGY AND METHOD OF ADMINISTRATION

Adjunct to oestrogen replacement therapy

- 10 mg daily for 10 to 12 days per month is adequate for most patients.
- 20 mg daily for 10 to 12 days per month should be used only in the event unacceptable withdrawal bleeding.
- In combination with cyclical oestrogen therapy, one film coated tablet of 10 dydrogesterone daily during the last 12 – 14 days of oestrogen therapy.

Progesterone deficiencies

- Dysmenorrhoea: 10 mg twice daily starting day 5 to day 25 of the cycle.
- Endometriosis: 10 mg twice daily from day 5 to day 25 of the cycle or continuously.
- Secondary amenorrhoea: an oestrogen once daily from day 1 to day 25 of the cycle, and Dytinum 10 mg twice daily from day 11 to day 25.
- Dosage in abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology (functional bleeding) such as submucous fibroids or uterine cancer.
 - To arrest functional bleeding: 10 to 20 mg (1 to 2 tablets) one or two times a day for five to ten days
 - To prevent further heavy bleeding: 10 to 20 mg (1 to 2 tablets) one or two times a day for the 11th day to 25th day of the menstrual cycle and repeated cyclically as needed
- Premenstrual syndrome: 10 mg twice daily from day 12 to day 26 of the cycle.
- Threatened abortion: 40 mg at once, then 10 mg every eight hours until symptoms remit.
- Dosage in habitual abortion associated with proven progesterone deficiency. Treatment should be started as soon as possible, preferably before conception. 10 mg dydrogesterone twice daily is to be given from the 11th to the 25th day of the cycle with continuous administration after conception. The treatment must be continued at any rate until the 20th week of pregnancy, then can be reduced gradually.
- Dosage in infertility due to luteal insufficiency: 10 mg dydrogesterone twice daily from the 11th to the 25th day of the cycle. The treatment is to be continued for at least 6 successive cycles. It is advised to continue this treatment during the first few months of a possible pregnancy, at dosages as are recommended for habitual abortion.
- Dytinum 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
- If used to prevent endometrial hyperplasia (in women using estrogens): Contraindications for use of oestrogens in combination with progestagens, such as dydrogesterone.
- Thrombophlebitis or thromboembolic disorders.
- Cerebrovascular or coronary artery disease, or a past history of these conditions.
- Hepatic disease or dysfunction, a history of cholestatic jaundice or pruritus of pregnancy and in Dubin-Johnson syndrome and Rotor syndrome.
- History of herpes of pregnancy.
- Sickle cell anaemia.
- Benign or malignant liver tumours which develop during the use of oral contraceptives

SPECIAL WARNINGS AND SPECIAL 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. 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, 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 Dydrogesterone in the indication "To prevent endometrial hyperplasia in women using estrogens":

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

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/m²);
- 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 contraindicated. 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) longterm 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 ischemic CVA was reported during treatment with continuous combined conjugated oestrogens with medroxyprogesterone acetate.

SIDE EFFECTS

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

MedDRA system organ class	Common >1/100, <1/10	Uncommon >1/1,000, <1/100	Rare >1/10,000, <1/1,000	Very rare <1/10,000 incl. isolated reports
Blood and the lymphatic system disorders				Haemolytic anaemia
Immune system disorders				Hypersensitivity reactions

Nervous system disorders	Migraines/ headache			
Hepatobiliary disorders		Alterations in liver function (with Jaundice, Asthenia or Malaise, and Abdominal pain)		
Skin and subcutaneous tissue disorders		Allergic skin reactions (e.g. rash, pruritus, urticaria)		Angioedema
Reproductive system and breast disorders	Breakthrough bleedings	Breast pain/ tenderness		
General disorders and administration site conditions				Oedema

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 Contraindications).

Psychiatric disorders

Depressed mood

Undesirable effects that are associated with an oestrogen-progestagen treatment, see also section Special warnings and precautions for use:

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

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 reported. 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.

Interaction with other medicaments 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 fetuses were exposed to dydrogesterone in around 9 million pregnancies¹. From spontaneous surveillance system until now, 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 (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 do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal, or postnatal development. Animal safety data are limited with respect to effects on parturition (see Preclinical safety data).

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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

STORAGE CONDITIONS:

- Store below 30°C in a dry place, protect from light.
- To be dispensed on the prescription of a registered medical practitioner only.
- Keep out of the reach of children.

PRESENTATION:

Dytinum 10mg Tablets are available as 2x10s blisters in a carton.

ہدایات:

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
دوا کو ۳۰ گری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں، روشنی سے بچائیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔

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