For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

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Dienogest Tablets 2 mg
Evafact™ *ईवाफैक्ट*

COMPOSITION

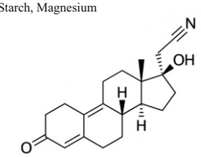
Each film coated tablet contains:

Dienogest IP	2 mg
Excipients	q.s.
Colour: Titanium Dioxide IP	

DESCRIPTION

Evafact™ is a white to off white tablet containing 2 mg Dienogest for oral use.
It also contains Lactose, Microcrystalline Cellulose, Starch, Magnesium Stearate, Talcum and Crospovidone as an excipients.

The chemical structure of Dienogest is as follows:



Dienogest is a nortestosterone derivative with an antiandrogenic activity of approximately one third of that of cyproterone acetate. Dienogest binds to the progesterone receptor of the human uterus with only 10% of the relative affinity of progesterone. Despite its low affinity to the progesterone receptor, Dienogest has a strong progestogenic effect *in vivo*. Dienogest has no significant androgenic, mineralocorticoid or glucocorticoid activity *in vivo*.

INDICATIONS

Evafact™ is indicated for the management of pelvic pain associated with endometriosis.

DOSAGE AND ADMINISTRATION

Tablet taking can start on any day of the menstrual cycle. The dosage of **Evafact™** is one tablet daily without any break, taken preferably at the same time each day with some liquid as needed. Tablets must be taken continuously without regard to vaginal bleeding. When a pack is finished the next one should be started without interruption. The efficacy of **Evafact™** may be reduced in the event of missed tablets, vomiting and/or diarrhoea (if occurring within 3-4 hours after tablet taking). In the event of missed tablet(s), the woman should take one tablet only, as soon as she remembers, and should then continue on the next day to take the tablet at her usual time. A tablet not absorbed due to vomiting or diarrhoea should likewise be replaced by one tablet. If a short acting, e.g. oral, hormonal treatment was prescribed before starting treatment with **Evafact™**; treatment may be started on the first day of menstrual bleeding after cessation of treatment. If a long-acting, i.e. injectable, hormonal treatment was administered before starting treatment with Dienogest, then Dienogest may be started once metabolism/excretion of the previously administered drug is expected to be completed.

USE IN SPECIAL POPULATIONS

Pregnant Women

The administration of Dienogest during pregnancy is contraindicated. If pregnancy occurs during treatment with Dienogest, further intake must be stopped. The data from a limited number of cases of exposure during pregnancy demonstrate that Dienogest does not show adverse effects on pregnancy or on the health of the fetus/newborn. No significant epidemiological data have been obtained to date. Preclinical data reveal no special risks on pregnancy, embryonic/fetal development, birth, or development after birth for humans.

Nursing Women

Dienogest is contraindicated during lactation. It is unknown if Dienogest is excreted in human milk. Data in animals have shown excretion in rat milk.

Geriatrics (> 65 years of age)

Dienogest is not indicated for use in the geriatric population.

Pediatrics (< 18 years of age)

Dienogest is not intended for use prior to menarche. The safety and efficacy of Dienogest in adolescents (menarche to 18 years) has not yet been established.

Renal Impairment

There are no data suggesting the need for a dosage adjustment in patients with renal impairment.

CONTRAINDICATIONS

Dienogest should not be used in women with any of the conditions listed below, which are partially derived from information on other progestin-only preparations. Should any of the conditions appear during the use of Dienogest, treatment must be discontinued immediately.

- Known or suspected pregnancy.
- Lactation.
- Active venous thromboembolic disorder.
- Arterial and cardiovascular disease, past or present (e.g. myocardial infarction, cerebrovascular accident, ischemic heart disease).
- Diabetes mellitus with vascular involvement.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Presence or history of liver tumors (benign or malignant).
- Known or suspected sex hormone-dependent malignancies.
- Undiagnosed abnormal vaginal bleeding.
- Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields.
- Current or history of migraine with focal aura.
- Hypersensitivity to Dienogest or to any ingredient in the formulation or component of the container.

WARNINGS AND PRECAUTIONS

General

Before initiating treatment with Dienogest, pregnancy must be excluded. During treatment, patients are advised to use non-hormonal methods of contraception (e.g. barrier method) if contraception is required. Hormonal methods of contraception should not be used in combination with Dienogest. As Dienogest is a progestin-only therapy, it can be assumed that special warnings and special precautions for use of other progestin-only therapies are valid for the use of Dienogest although not all of the warnings and precautions are based on respective findings in the clinical studies with Dienogest. Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. Women should be counseled not to smoke.

Bone mineral density

In patients who are at an increased risk of osteoporosis a careful risk-benefit assessment should be performed before starting Dienogest because endogenous estrogen levels are moderately decreased during treatment with Dienogest. Currently, long-term data on bone mineral density (BMD) and risk of fractures in users of Dienogest are not available. BMD was assessed in 21 patients before and after 6 months of treatment with Dienogest and there was no reduction of mean BMD. In 29 patients treated with leuprolide acetate (LA), a mean reduction of 4.04% ± 4.84% was noted after the same period (different between groups = 4.29%; 95% CI: 1.93 – 6.66; P < 0.0003).

Carcinogenesis and mutagenesis

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using oral contraceptives (OCs), mainly estrogen-progestin preparations. The excess risk gradually disappears during the course of the 10 years after cessation of combined oral contraceptives (COC) use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall lifetime risk of breast cancer. The risk of having breast cancer diagnosed in progestin-only pill users is possibly of similar magnitude to that associated with COC. However, for progestin-only preparations, the evidence is based on much smaller populations of users and therefore is less conclusive than that for COCs. These studies do not provide evidence of causality. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in OC users, the biological effects of OCs, or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users; however a small proportion of younger women appear to develop more aggressive cancers after using OCs than never-users. Regular breast exams should be done in patients using Dienogest. Any irregularity or anomaly of the breast should be adequately investigated (e.g. by mammography or ultrasound). In rare cases, benign tumors and, even more rarely, malignant liver tumors have been reported in users of hormonal substances, such as the one contained in Dienogest. In isolated cases, these tumors have led to life-threatening intra-abdominal hemorrhages.

Cardiovascular

From epidemiological studies, there is little evidence for an association between progestin-only preparations and an increased risk of myocardial infarction or cerebral thromboembolism. The risk of cardiovascular and cerebral events is rather related to increasing age, hypertension, and smoking. In women with hypertension, the risk of stroke may be slightly increased by progestin-only preparations. Some studies indicate that there may be a slightly, but not statistically significant, increased risk of venous thromboembolism (deep venous thrombosis, pulmonary embolism) associated with the use of progestin-only preparations. Generally recognized risk factors for venous thromboembolism (VTE) include a positive personal or family history (VTE in a sibling or a parent at a relatively early age), age, obesity, prolonged immobilization, major surgery, or major trauma. In cases of long-term immobilization it is advisable to discontinue the use of Dienogest (in the case of elective surgery, at least 4 weeks in advance) and not to resume treatment until 2 weeks after complete remobilization. The increased risk of thromboembolism in the puerperium must be considered. Treatment with Dienogest should be discontinued immediately if there is suspicion or symptoms of an arterial or venous thrombotic event. Dienogest generally does not appear to affect blood pressure in normotensive women. However, if sustained clinically significant hypertension develops during the use of Dienogest, it is advisable to stop treatment with Dienogest and treat the hypertension.

Hepatic

Dienogest is contraindicated in patients with present or past severe hepatic disease.

Renal

Dienogest has not been studied in patients with impaired renal function. However, no special risk for these patients is expected since Dienogest is almost completely metabolized before excretion and the metabolites are pharmacologically inactive.

Pancreatic

Dienogest may slightly induce peripheral insulin resistance and glucose intolerance. Diabetic women, especially those with a history of gestational diabetes mellitus, should be carefully observed while taking Dienogest.

Psychiatric

Patients who have a history of depression should be carefully observed. Dienogest should be discontinued if clinically relevant depression occurs or if pre-existing depression is aggravated during treatment.

Sexual function/Reproduction

Although ovulation is inhibited in the majority of patients during treatment with Dienogest, it is not intended for use as a contraceptive. The menstrual cycle returns to pretreatment characteristics within 2 months after cessation of treatment with Dienogest. If contraception is required, a non-hormonal method (e.g. barrier method) should be used. Hormonal methods of contraception should not be used in combination with Dienogest. Pregnancies that occur among users of progestin-only preparations for contraception are more likely to be ectopic than are pregnancies among users of combined oral contraceptives. Therefore, in women with a history of extrauterine pregnancy or an impairment of fallopian tube function, the use of Dienogest should be considered only after carefully weighing the benefits against the risks. Persistent ovarian follicles (often referred to as functional ovarian cysts) may occur during the use of Dienogest. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain.

Changes in bleeding pattern

Dienogest treatment affects the menstrual bleeding pattern in the majority of women.

Uterine bleeding, for example in women with adenomyosis or uterine leiomyomas (fibroids), may be aggravated with the use of Dienogest. If bleeding is heavy and continues over time, this may lead to anemia (severe in some cases). Discontinuation of Dienogest should be considered in such cases.

Dienogest is expected to exhibit typical progestogenic effects on the endometrium by reducing estrogen levels which are the main growth stimulus for endometrial tissue. This may result in reduced endometrial thickness and an atrophic endometrium during treatment. Menstrual cycle returns to pretreatment characteristics within 2 months after cessation of treatment with Dienogest. Abnormal vaginal bleeding (e.g. prolonged and/or heavy) should be thoroughly investigated by pelvic ultrasound, endometrial biopsy or hysteroscopy.

Skin

Recurrence of cholestatic jaundice and/or pruritus which first occurred during pregnancy or with previous use of sex steroids necessitates the discontinuation of Dienogest.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking Dienogest.

DRUG INTERACTIONS

Overview

Dienogest should not be prescribed simultaneously with other steroids including danazol. Progestins including Dienogest are metabolized mainly by the cytochrome P450 3A4 system (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect progestin drug metabolism. An increased clearance of sex hormones due to enzyme induction may reduce the therapeutic effect of Dienogest. A reduced clearance of sex hormones due to enzyme inhibition may increase the exposure to Dienogest and may result in undesirable effects.

Some medicines can have an influence on the blood levels of Dienogest and can make it less effective, or can cause undesirable effects. These include:

- Medicines used for the treatment of epilepsy (e.g. phenytoin, barbiturates, primidone, carbamazepine, oxcarbazepine, topiramate, felbamate); tuberculosis (e.g. rifampicin); HIV and Hepatitis C Virus infections (so-called protease inhibitors and non-nucleoside reverse transcriptase inhibitors such as ritonavir, nevirapine, efavirenz); fungal infections (griseofulvin, ketoconazole).
- The herbal remedy St. John's wort.

Drug-Drug Interactions

Substances increasing the clearance of sex hormones (diminished efficacy by enzyme induction)

Substances increasing the clearance of sex hormones include phenytoin, barbituates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John's wort. Enzyme induction can be observed after a few days of treatment. Maximum enzyme induction is generally seen within a few weeks. After the cessation of drug therapy, enzyme induction may be sustained for about 4 weeks.

Substances with variable effects on the clearance of sex hormones

When co-administered with sex hormones, many HIV/HCV protease inhibitors and nonnucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of the progestin. These changes may be clinically relevant in some cases.

Substances decreasing the clearance of sex hormones (enzyme inhibitors)

Dienogest is a substrate of cytochrome P450 (CYP) 3A4. Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. ketoconazole, itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the progestin.

Effects of Dienogest on other medications

Based on *in vitro* inhibition studies, it is unlikely that Dienogest will have clinically relevant effects on the cytochrome P450 enzyme-mediated metabolism of other medications.

Drug-Food Interactions

The bioavailability of Dienogest was unaffected by a high fat meal. Dienogest can be taken with or without food.

Drug-Herb Interactions

Herbal products containing St. John's wort (Hypericum perforatum) may induce CYP3A4 enzymes and can result in increased clearance of sex hormones.

Drug-Laboratory Interactions

The use of progestins may influence the results of certain laboratory tests (e.g. gonadotropin, endogenous hormones). The results of certain endocrine and liver function tests may be affected by progestin-containing products:

- Impaired glucose tolerance;
- Reduced serum folate concentration;
- Change in plasma lipoprotein levels.

The results of the above laboratory tests should not be considered reliable unless therapy has been discontinued for 2 to 4 weeks. However, no significant impact on standard laboratory parameters, including hematology, blood chemistry, liver enzymes, lipids and HbA1C was reported during treatment with Dienogest for up to 15 months.

UNDESIRABLE EFFECTS

Undesirable effects are more common during the first months after start of intake of Dienogest, and subside with duration of treatment. The following undesirable effects have been reported in users of Dienogest. The most frequently reported undesirable effects during treatment that were considered at least possibly related to Dienogest were headache (9.0%), breast discomfort (5.4%), depressed mood (5.1%), and acne (5.1%).

Common (> 1/100)

Weight increase depressed mood, sleep disorder, nervousness, loss of libido, altered mood, headache, migraine, nausea, abdominal pain, flatulence, abdominal distension, vomiting, acne, alopecia, back pain, breast discomfort, ovarian cyst, hot flushes, uterine/vaginal bleeding, including spotting, irritability.

Uncommon (>1/1,000 to < 1/100)

Anemia, increased appetite, anxiety, depression, mood swings, autonomic nervous system imbalance, disturbance in attention, dry eye, tinnitus, palpitations, unspecified circulatory system disorder, hypotension, dyspnea, abdominal discomfort, constipation, diarrhea, gastrointestinal inflammation, gingivitis, dermatitis, dry skin, onychoclasis, photosensitivity reaction, pigmentation disorder, pruritus, back pain, bone pain, heaviness in extremities, muscle spasms, pain in extremity, urinary tract infection, breast induration, breast mass, fibrocystic breast, disease, genital discharge, hot flush, pelvic pain, vaginal candidiasis, vulvovaginal dryness, edema.

OVERDOSAGE

A clinical study has shown that 20 to 30 mg Dienogest per day (10 to 15 times the recommended dose of Dienogest) over 24 weeks of use in women was generally well tolerated. There is no specific antidote to a Dienogest overdose and further treatment should be symptomatic, based on the pharmacological action of Dienogest.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Dienogest reduces the endogenous production of estradiol and thereby suppresses the trophic effects of estradiol on both the eutopic and ectopic endometrium. When given continuously, Dienogest leads to a hyperprogestogenic and moderately hypoestrogenic endocrine environment causing initial decidualization of endometrial tissue. Additional direct antiproliferative, immunologic and antiangiogenic effects seem to contribute to the inhibitory action of Dienogest on cell proliferation and to the reduction of pelvic pain associated with endometriosis.

Bone Mineral Density

Bone mineral density (BMD) was assessed in 21 patients before and after 6 months of treatment and there was no reduction in mean BMD.

Ovarian Function

In a study reported in 20 healthy women, a daily dose of 2 mg Dienogest has been shown to induce an anovulatory state after 1 month of treatment. Dienogest has not been tested for contraceptive efficacy. Dienogest is not intended for use as a contraceptive. If contraception is required, a nonhormonal method should be used.

Endogenous estrogen levels are only moderately suppressed during treatment with Dienogest. Based on available data, the menstrual cycle returns to pretreatment characteristics within 2 months after cessation of treatment with Dienogest.

Hypothalamo-Hypophyseal Function

Administered exogenously and continuously, progestins reduce the frequency and increase the amplitude of pulsatile GnRH release, which results in a reduction of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion.

Pharmacokinetics

Pharmacokinetics of Dienogest are not influenced by sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG) levels. Following daily ingestion, drug serum levels increase about 1.24-fold reaching steady-state conditions after 4 days of treatment. The pharmacokinetics of Dienogest after repeated administration of Dienogest Tablets can be predicted from single-dose pharmacokinetics. The pharmacokinetics of Dienogest are dose-proportional and linear within the dose range of 1 to 8 mg. There is minimal accumulation with repeated administration (accumulation ratio 1:24) and neither the time to maximum concentration nor the terminal half-life are altered compared to single-dose administration.

Absorption

Orally administered Dienogest is rapidly and almost completely absorbed. Peak serum concentrations of 47 ng/mL are reached at about 1.5 hours after single ingestion of 2 mg. Bioavailability is about 91%. The pharmacokinetics of Dienogest are dose-proportional within the dose range of 1 to 8 mg.

Distribution

Dienogest is bound to serum albumin and does not bind to sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG). 10% of the total serum drug concentrations are present as free steroid; 90% are nonspecifically bound to albumin. The apparent volume of distribution (Vd/F) of Dienogest is 40 L.

Metabolism

Dienogest is completely metabolized by the known pathways of steroid metabolism, with the formation of metabolites which are mostly inactive endocrinologically. Based on *in vitro* and *in vivo* studies, CYP3A4 is the major enzyme involved in the metabolism of Dienogest. The metabolites are excreted very quickly; therefore in plasma, unchanged Dienogest is the dominating fraction. The metabolic clearance rate from serum (Cl/F) is 64 mL/min.

Excretion

Dienogest serum levels decrease in 2 phases. The terminal disposition phase is characterized by a half-life of approximately 9 to 10 hours. Dienogest is excreted in the form of inactive metabolites which are excreted at a urinary to fecal ratio of about 3:1 after oral administration of 0.1 mg/kg. The half-life of urinary metabolites excretion is 14 hours. Following oral administration, most of the drug is excreted in the urine within the first 24 hours. Approximately 86% of the administered dose is eliminated within 6 days.

INCOMPATIBILITIES

Already discussed in Drug Interactions.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects on the ability to drive and use machines have been observed in users of products containing Dienogest.

SHELF LIFE:

18 month from the date of Manufacturing.

STORAGE AND HANDLING INSTRUCTIONS:

Store protected from light & moisture, at a temperature not exceeding 25°C.
Keep out of reach of children.

PRESENTATION

Evafact™ is available as Alu-Alu blister pack of 10 tablets individually packed in a carton along with a pack insert. 10 such cartons are packed in 1 outer carton.

Manufactured in India by:
Synokem Pharmaceuticals Ltd.
Plot No.:- 56-57, Sector-6A, IIE (SIDCUL), Ranipur, Haridwar-249403 (Uttarakhand)

Size : 8.228 "x10.63"

To Report Suspected Adverse Reactions, Contact Bharat Serums and Vaccines at pv@bharatserums.com or visit the website www.bharatserums.com / adverse.html

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