# Dienomax

## Dienogest 2 mg

Urufarma

LI-0000-00

**Formula:**
Each coated tablet contains dienogest 2 mg and excipients (q.s.)

**Indications:**
Treatment of endometriosis.

**Posology and method of administration**
The treatment involves taking one tablet daily, without breaks, preferably at the same time every day. Take the tablet with or without food.
Take the tablets without taking breaks, regardless of vaginal bleeding. When you finish a pack, start a new pack without any break in between.
There is no available experience with dienogest treatment over 15 months in patients with endometriosis.
You can start the treatment at any point of the menstrual cycle. Before starting the treatment with dienogest, stop taking any other hormonal contraceptive. If you require a birth control method, use a non-hormonal contraceptive (a barrier contraceptive, such as a condom).
The efficacy of dienogest can decrease if you miss taking a tablet or if you experience vomiting or diarrhoea (if these occur within 3 to 4 hours after taking the tablet). If you forget to take one or more tablets, take only one tablet as soon as you remember it. Then, continue taking the tablets as usual the next day. Moreover, if you do not absorb the tablet due to vomiting or diarrhoea, take another tablet.
*Paediatric population*: Dienogest is not indicated in girls before their menarche.
The safety and efficacy of dienogest has been studied in a 12-month uncontrolled clinical trial in 111 adolescent women (aged 12 to 18 years) with clinically confirmed or clinically suspected endometriosis.
*Geriatric population*: There are no relevant indications for the use of dienogest in the geriatric population.
*Patients with hepatic impairment*: Dienogest is contraindicated in patients with past or present severe liver disease.
*Patients with renal impairment*: There is no information to suggest the need for a dosage adjustment in patients with renal impairment.

**Contraindications**
Dienogest should not be used in the presence of any of the conditions listed below, which are derived from information on other progestogen-only preparations. If any of these conditions occur during the use of dienogest, stop the treatment immediately.
- active venous thromboembolic disorder.
- existence or history of arterial and cardiovascular disease (e.g., myocardial infarction, stroke, ischaemic heart disease)
- diabetes mellitus with vascular involvement
- existence or history of severe liver disease, provided that the values of liver function tests have not returned to normal
- existence or history of liver tumours (benign or malignant)
- sex-hormone-dependent malignancies, known or suspected.
- undiagnosed vaginal bleeding
- Hypersensitivity to the drug substance or any of the other components of the formula.

**Precautions and warnings**
Dienomax is a progestogen-only preparation. Therefore, warnings and precautions that apply to the use of other progestogen-only preparations are probably also valid for Dienomax, even though not all warnings and precautions are based on the respective results from clinical trials using dienogest.
If any of the following conditions/risk factors are present or worsening, the benefits of use should be weighed against the potential risks for the individual woman before initiating or continuing treatment with dienogest.
- *Heavy uterine bleeding*: Uterine bleeding, for instance, in women with adenomyosis or uterine leiomyomas, may be aggravated using dienogest. If bleeding is heavy and prolonged, it can lead to anaemia (severe in some cases). In case of anaemia, discontinuation of dienogest treatment should be considered.
- *Changes in bleeding pattern*: Most patients treated with dienogest experience changes in their menstrual bleeding pattern.
- *Circulatory disorders*: In epidemiological studies there is little evidence of a link between progestogen-only preparations and an increased risk of myocardial infarction or cerebral thromboembolism. In contrast, the risk of cardiovascular and cerebral events is related to older age, hypertension, and smoking. In women with hypertension, progestogen-only preparations may slightly increase the risk of stroke. Some studies suggest that there may be a slight, but not statistically significant, increase in the risk of venous thromboembolism (deep vein thrombosis, pulmonary embolism) associated with the use of preparations that only contain progestogens. Generally recognised risk factors for venous thromboembolism include a personal or family history of the condition (venous thromboembolism in a sibling or parent at a relatively young age), age, obesity, prolonged immobilisation, major surgery, or major trauma. In case of prolonged immobilisation, it is advisable to suspend the use of dienogest (in case of elective surgery, at least four weeks in advance) and not to resume it until two weeks after full recovery of mobility.
The increased risk of thromboembolism in the puerperium should be considered.
Treatment should be discontinued immediately in case of an arterial or venous thrombotic incident, or these conditions are suspected.
- *Tumours*: A meta-analysis of 54 epidemiological studies found that there is a slightly increased relative risk (RR = 1.24) of breast cancer being diagnosed in women taking oral contraceptives (COCs), mainly oestrogen-progestogen preparations. This increased risk gradually disappears within ten years of stopping the use of combined oral contraceptives (COCs). Since breast cancer is rare in women under the age of 40, the increase in diagnosed cases of breast cancer in current and recent COCs users is small relative to the overall risk of breast cancer. The risk of being diagnosed with breast cancer in users of progestogen-only preparations is possibly similar in magnitude to that associated with COCs. However, for progestogen-only preparations, the evidence is based on much smaller populations of users and is therefore less conclusive than for COCs. These studies do not provide evidence on causality. The observed pattern of increased risk may be due to earlier diagnosis of breast cancer in COC users, the biological effects of COCs, or a combination of both. Breast cancers diagnosed in women who have used a COC are usually less clinically advanced than those diagnosed in women who have never used COCs.
In rare occasions, benign liver tumours have been reported (and more rarely, malignant tumours as well) in users taking hormonal substances such as the one in Dienomax. In isolated cases, these tumours have resulted in life-threatening intra-abdominal haemorrhages. The possibility of a liver tumour should be considered in the differential diagnosis of women taking dienogest who have severe upper abdominal pain, liver enlargement, or signs of intra-abdominal bleeding.
- *Osteoporosis*: Changes in bone mineral density (BMD):
The use of dienogest in teenagers (aged 12 to 18 years) during a 12-month treatment period was associated with a decrease in bone mineral density (BMD) at the lumbar spine (L2 to L4). The mean relative change in BMD from baseline to end of treatment (EOT) was −1.2% with a range between −6% and 5% (95% CI: −1.70% and −0.78%, n = 103). Repeat measurements at 6 months after EOT in a subgroup with decreased BMD values showed a trend towards recovery. (Mean relative change from baseline: −2.3% at EOT and −0.6% at 6 months after EOT with a range between −9% and 6% (95% CI: −1.20% and 0.06% (n = 60)).
BMD loss is of particular concern during adolescence and early adulthood, a critical period of bone development. It is not known whether decreased BMD in this population may reduce peak bone mass and increase fracture risk in the future. A careful benefit-risk assessment should be performed in patients at increased risk of osteoporosis before starting dienogest because endogenous oestrogen levels decrease moderately during dienogest treatment.
Adequate calcium and vitamin D intake, both from the diet and from dietary supplements, is important for bone health in women of all ages.
- *Other conditions*: Patients with a history of depression should be followed closely and the drug should be discontinued if depression recurs to a severe extent.
In general, dienogest does not seem to affect the blood pressure of women with normal blood pressure. However, if clinically significant and sustained hypertension occurs during the use of dienogest, it is advisable to withdraw this medicine and treat the hypertension.
Dienogest should be discontinued if there is recurrence of cholestatic jaundice and/or pruritus that first appeared during pregnancy or with previous use of sex steroids.
Dienogest may have a slight effect on peripheral insulin resistance and glucose tolerance. Diabetic women, especially those with a history of gestational diabetes mellitus, should be carefully monitored while taking dienogest.
Occasionally, chloasma may occur, especially in women with a history of chloasma during pregnancy. Women with a tendency to chloasma should avoid exposure to sun or ultraviolet radiation while taking dienogest.
Pregnancies in users of progestogen-only contraceptive preparations are more likely to be ectopic than pregnancies in women taking combined oral contraceptives. Therefore, the use of dienogest should be decided only after careful weighing of benefits and risks in women with a history of extrauterine pregnancy or impaired tubular function.
Persistent ovarian follicles (often called functional ovarian cysts) may occur during the use of dienogest. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain.
This medicine contains lactose. Patients with hereditary intolerance to galactose, Lapp lactase insufficiency, or issues with absorption of glucose or galactose should not take this medicine.

**Interaction with other medicines and other forms of interaction**
- *Effects of other medicines on dienogest*
Progestogens, including dienogest, are metabolised mainly by the cytochrome P450 3A4 (CYP3A4) system located in the intestinal mucosa and liver. Therefore, CYP3A4 inducers or inhibitors may affect progestogen metabolism.
Increased sex hormone clearance due to enzyme induction may reduce the therapeutic effect of dienogest and may lead to adverse reactions, such as changes in the uterine bleeding profile. Decreased sex hormone clearance due to enzyme inhibition may increase exposure to dienogest and may lead to adverse reactions.

<u>- Substances that increase the plasma clearance of sex hormones (e.g., decreased efficacy due to enzyme induction):</u>
phenytoin, barbiturates, primidone, carbamazepine, rifampicin and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John's wort (*Hypericum perforatum*).
Generally, peak enzyme induction is found within a few weeks. After discontinuing the treatment, enzyme induction may persist for 4 weeks.
The effect of rifampicin, a CYP3A4 inducer, was studied in healthy postmenopausal women. Concomitant administration of rifampicin with estradiol valerate tablets and dienogest resulted in significant decreases in steady-state concentrations and systemic exposures to dienogest and estradiol. Steady-state systemic exposure to dienogest, as determined by AUC (0-24 h), was reduced by 83%; exposure to estradiol, under the same conditions, was reduced by 44%.

<u>- Substances with variable effects on plasma clearance of sex hormones:</u>
When coadministered with sex hormones, many combinations of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV inhibitors, may increase or decrease plasma progestogen concentrations. The net effect of these changes may be clinically relevant in some cases.

<u>- Substances that decrease plasma clearance of sex hormones (enzyme inhibitors):</u> dienogest is a substrate of CYPP450 CYP3A4.
The clinical relevance of potential interactions with enzyme inhibitors is unknown.
Concomitant administration of potent CYP3A4 inhibitors may increase plasma concentrations of dienogest.
Coadministration with ketoconazole, a potent CYP3A4 inhibitor, resulted in a 2.9-fold increase in the steady-state AUC (0-24 h) of dienogest. Concomitant administration with erythromycin, a moderate CYP3A4 inhibitor, increased the AUC (0-24h) of dienogest at steady state by 1.6-fold.

*Effects of dienogest on other medicines*
Based on *in vitro* inhibition studies, it is unlikely that there is a clinically relevant interaction of dienogest with the metabolism of other medicines mediated by the cytochrome P450 enzyme.

*- Laboratory tests*
The use of oral progestogens may affect the results of certain laboratory tests, such as biochemical parameters of liver, thyroid, adrenal, and renal function, plasma levels of transport proteins (e.g., corticosteroid transport globulin and lipid/lipid-protein fractions), parameters of carbohydrate metabolism, and parameters of coagulation, and fibrinolysis. Generally, changes remain within the normal limits.

**Fertility, pregnancy, and breastfeeding**
*Pregnancy*
There are limited data on the use of dienogest in pregnant women. Animal studies suggest no direct or indirect harmful effects in terms of reproductive toxicity.
However, dienogest should not be given to pregnant women because it is not necessary to treat endometriosis during pregnancy.
*Breastfeeding*
Treatment with dienogest is not recommended during breastfeeding. It is not known whether dienogest is excreted in human milk. Animal data show that dienogest is excreted in rat milk.
A decision on whether to discontinue breastfeeding or discontinue dienogest treatment should be made after considering the benefit of breast-feeding for the child and the benefit of treatment for the mother.
*Fertility*
Based on available data, ovulation is inhibited in most patients during treatment with dienogest. Nevertheless, dienogest is not a contraceptive. If contraception is required, a non-hormonal method should be used.
Based on available data, the menstrual cycle returns to normal after 2 months of discontinuing dienogest treatment.

**Adverse reactions**
Adverse reactions are more frequent during the first months after starting treatment with dienogest and subside with continued treatment. There may be changes in the pattern of bleeding, such as spotting, irregular bleeding, or amenorrhoea. The following adverse reactions have been reported in patients taking dienogest.
The most frequently reported adverse reactions with dienogest treatment are headache (9.0%), breast discomfort (5.4%), depressed mood (5.1%), and acne (5.1%).
In addition, most patients treated with dienogest experience changes in the pattern of their menstrual bleeding. These patterns were systematically assessed using patient diaries and analysed using the WHO 90-day reference period method. During the first 90 days of dienogest treatment, the following bleeding patterns were observed (n = 290; 100%): amenorrhoea (1.7%), infrequent bleeding (27.2%), frequent bleeding (13.4%), irregular bleeding (35.2%), prolonged bleeding (38.3%), normal bleeding, i.e., none of the above categories (19.7%).

During the fourth reporting period, the following bleeding patterns were observed (n = 149); 100%): amenorrhoea (28.2%), infrequent bleeding (24.2%), frequent bleeding (2.7%), irregular bleeding (21.5%), prolonged bleeding (4.0%), normal bleeding, i.e., none of the above categories (22.8%). Patients only occasionally reported changes in menstrual bleeding pattern as adverse reactions (see adverse reaction table).
The following table lists the frequencies of adverse drug reactions by MedDRA System Organ Class (MedDRA SOCs) reported with dienogest. The adverse reactions are listed in decreasing order of frequency. Adverse events are defined as common (= 1/100 to < 1/10) and uncommon (= 1/1.000 to < 1/100). Frequencies are based on pooled data from four clinical studies with 332 patients (100%).

| *SYSTEM ORGAN CLASS* | *COMMON* | *UNCOMMON* |
|---|---|---|
| Blood and lymphatic system disorders. | | *Anaemia* |
| Metabolic and nutrition disorders. | *Weight gain* | *Weight loss*<br>*Increased appetite* |
| Psychiatric disorders | *Depressed mood,*<br>*Sleep disturbance,*<br>*Nervousness,*<br>*Decreased libido*<br>*Mood swings* | *Anxiety*<br>*Depression*<br>*Mood liability* |
| Nervous system disorders | *Headaches*<br>*Migraine* | *Imbalance of the autonomic nervous system*<br>*Attention disorder* |
| Eye disorders | | *Dry eye* |
| Ear and labyrinth disorders | | *Tinnitus* |
| Heart disorders | | *Non-specific circulatory system disorder*<br>*Palpitations* |
| Vascular disorders | | *Hypotension* |
| Respiratory, thoracic and mediastinal disorders | | *Dyspnoea* |
| Gastrointestinal tract disorders | *Nausea*<br>*Abdominal pain*<br>*Flatulence*<br>*abdominal distension,*<br>*Vomiting* | *Diarrhoea*<br>*Constipation*<br>*Abdominal discomfort*<br>*Gastrointestinal inflammation*<br>*Gingivitis* |
| Skin and connective tissue disorders | *Acne*<br>*Alopecia* | *Dry skin*<br>*Hyperhidrosis*<br>*Pruritus*<br>*Hirsutism*<br>*Onychoclasia*<br>*Dandruff*<br>*Dermatitis*<br>*Abnormal hair growth,*<br>*Photosensitivity reaction*<br>*Pigmentation disorder* |
| Musculoskeletal and connective tissue disorders | *Lumbar pain* | *Bone pain*<br>*Muscle spasms*<br>*Limb pain*<br>*Leaden paralysis* |
| Kidney and urinary disorders | | *Urinary tract infection* |
| Reproductive and breast disorders | *Breast tenderness*<br>*Ovarian cyst*<br>*Hot flushes*<br>*Uterine or vaginal bleeding, including spotting* | *Vaginal candidiasis*<br>*Vulvovaginal dryness*<br>*Vaginal discharge*<br>*Pelvic pain*<br>*Atrophic vulvovaginitis*<br>*Breast mass*<br>*Fibrocystic breast disease*<br>*Breast induration* |
| General disorders and alterations at the site of administration | *Asthenia*<br>*Irritability* | *Oedema* |

**Bone mineral density decrease**
In an uncontrolled clinical trial of 111 adolescent females (aged 12 to 18 years) who were treated with dienogest, BMD measurements were performed on 103 females. Approximately 72% of these study participants experienced a decrease in BMD of the lumbar spine (L2 to L4) after 12 months of use.

**Overdose**
Acute toxicity studies with dienogest have not shown a risk of acute adverse reactions in case of accidental ingestion of multiple daily therapeutic doses. The is no specific antidote. Daily intake of 20 to 30 mg of dienogest (a 10 to 15-fold higher dose than Dienomax) for periods over 24 weeks was well tolerated. In case of poisoning, seek medical assistance immediately.

**Presentation:**
Pack containing 28 tablets.
Keep at room temperature (15 - 30°C).
Keep out of the reach of children.

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