UNILAB

Dienogest

RILIZ™

2 mg Film-coated Tablet
Progestogen

℞

FORMULATION
Each film-coated tablet contains:
Dienogest, Ph. Eur. …….. 2 mg

PRODUCT DESCRIPTION
White, round film-coated tablet

CLINICAL PHARMACOLOGY
PHARMACODYNAMICS
Dienogest is a nortestosterone derivative with no androgenic but rather 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*.

Dienogest acts on endometriosis by reducing 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 hypoestrogenic, hypergestagenic endocrine environment causing initial decidualization of endometrial tissue followed by atrophy of endometriotic lesions.

Additional direct antiproliferative, immunologic and antiangiogenic effects seem to contribute to the inhibitory action of dienogest on cell proliferation.

PHARMACOKINETICS
Dienogest is rapidly and almost completely absorbed after oral administration. Peak serum concentrations of 47 ng/mL are reached within 1.5 hours after single administration. The bioavailability of dienogest is about 91%. Food does not affect the bioavailability of dienogest. The pharmacokinetics of dienogest is dose-proportional within the dose range of 1 to 8 mg.

The pharmacokinetics of dienogest are not influenced by sex hormone binding globulin (SHBG) levels. Following daily intake, drug serum levels increase about 1.24-fold reaching steady-state conditions after 4 days of treatment. The pharmacokinetics of dienogest after repeated administration can be predicted from single dose pharmacokinetics of the drug.

Dienogest is bound to serum albumin and does not bind to SHBG or corticoid binding globulin (CBG). About 10% of the total serum drug concentration is present as free steroid, 90% is non-specifically bound to albumin.

The apparent volume of distribution (Vd/F) of dienogest is 40 L.

Dienogest is completely metabolized by the known pathways of steroid metabolism, with the formation of endocrinologically mostly inactive metabolites. 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 so that in plasma unchanged dienogest is the dominating fraction.

The metabolic clearance rate from serum (CL/F) is 64 mL/min.

Dienogest serum levels decrease in two phases. The terminal disposition phase is characterized by a half-life of approximately 9 to 10 hours. Dienogest is excreted in form of 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, approximately 86% of the dose administered is eliminated within 6 days, the bulk of this amount excreted within the first 24 hours, mostly with the urine.

Dienogest has not been studied in patients with renal or hepatic impairment.

INDICATION
Treatment of endometriosis

DOSAGE AND MODE OF ADMINISTRATION
General Dosing Recommendations:
• Dienogest tablets are intended for continuous administration in women for the treatment of endometriosis. There are reported longterm studies of dienogest use for more than 15 months.
• Drug administration can be started on any day of the menstrual cycle.
• May be taken with or without food

Recommended Dose and Dose Adjustment
Adults: Orally, 1 tablet daily without a break, preferably at the same time each day, with some liquid as needed.
• Tablets must be taken continuously regardless of any vaginal bleeding.
• When a pack is finished, the next one should be started without interruption.
Or, as prescribed by a physician.

Missed Dose
The efficacy of dienogest may be reduced in the event of missed tablets, vomiting and/or diarrhea (if occurring within 3 to 4 hours after the tablet is taken). In the event of a missed dose, the patient should take 1 tablet only as soon as possible and then continue to take the next tablet at her usual time the next day. A tablet not absorbed due to vomiting or diarrhea should likewise be replaced by 1 tablet. The patient should not take more than 1 tablet per day.

Dosage in Patients with Hepatic Impairment: Dienogest is contraindicated in patients with existing or history of hepatic disease.

Dosage in Patients with Renal Impairment: No dosage adjustment is necessary 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 progestogen-only preparations. Should any of the conditions appear during the use of dienogest, treatment must be discontinued immediately.

• Hypersensitivity to dienogest or to any component of the product
• Known or suspected pregnancy
• Breastfeeding
• 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

WARNINGS AND PRECAUTIONS
General
Before initiating treatment with dienogest, pregnancy must be excluded. Dienogest is not a contraceptive. If contraception is desired during treatment, hormonal methods of contraception should not be used in combination with dienogest.

As dienogest is a progestogen-only therapy, it can be assumed that special warnings and special precautions for use of other progestogen-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.

If any of the conditions/risk factors mentioned below is present or deteriorates, an individual risk-benefit analysis should be done before treatment with dienogest can be started or continued. Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. Smoking may also increase the risk of bone mineral density decline. Women should be advised not to smoke.

Serious Uterine Bleeding
Uterine bleeding, for example in women with adenomyosis uteri or uterine leiomyomata, may be aggravated with the use of dienogest. If bleeding is heavy and continuous over time, this may lead to anemia (severe in some cases). In the event of anemia, discontinuation of dienogest should be considered.

Changes in Bleeding Pattern
The majority of women treated with dienogest experience changes in their menstrual bleeding pattern (see Undesirable Effects).

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.

The 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.

Thrombotic and Vascular Events
From epidemiological studies there is little evidence for an association between progestogen-only preparations and an increased risk of myocardial infarction or cerebral thromboembolism. The risk of cardiovascular and cerebral events is related to increasing age, hypertension, and smoking. In women with hypertension the risk of stroke may be slightly enhanced by progestogen-only preparations.

Although not statistically significant, some studies indicate that there may be a slightly increased risk of venous thromboembolism (deep venous thrombosis, pulmonary embolism) associated with the use of progestogen-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 case of long-term immobilization it is advisable to discontinue the use of dienogest (in the case of elective surgery at least four 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 should be stopped at once if there are symptoms of an arterial or venous thrombotic event or suspicion thereof.

Breast Cancer
A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR of 1.24) of having breast cancer diagnosed in women who are currently using oral contraceptives (OCs), mainly using estrogen-progestogen preparations. The excess risk gradually disappears during the course of the 10 years after cessation of combined OC (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 risk of breast cancer. The risk of having breast cancer diagnosed in users of progestogen-only preparations is possibly of similar magnitude to that associated with COC. However, for progestogen-only preparations, the evidence is based on much smaller populations of users and so is less conclusive than that for COCs. These studies do not provide evidence for causation. 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 users of OCs tend to be less advanced clinically than the cancers diagnosed in those who have never used OCs.

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).

Liver Tumor
In rare cases, benign liver 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. A hepatic tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intraabdominal hemorrhage occur in women taking dienogest.

Osteoporosis and Changes in 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. There are no long-term data available on bone mineral density (BMD) and risk of fractures in patients taking dienogest.

In adult patients, BMD was assessed before and after 6 months of treatment with dienogest and there was no reduction of mean BMD. In adolescents (12 to <18 years of age), the use of dienogest over a treatment period of 12 months was associated with a mean decrease in BMD in the lumbar spine of 1.2%. After cessation of treatment, BMD increased towards pretreatment levels over a period of 6 months.

Plateauing or loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if BMD decrease in this population will reduce peak bone mass and increase the risk for fracture in later life.

Adequate intake of calcium and vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

Chloasma
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.

Diabetes
Dienogest may have a slight effect on peripheral insulin resistance and glucose tolerance. Women with diabetes, especially those with a history of gestational diabetes mellitus, should be carefully observed while taking dienogest.

Depression
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.

Ectopic Pregnancy
Pregnancies that occur among users of progestogen-only preparations used 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 tube function, the use of dienogest should be decided only after carefully weighing the benefits against the risks.

Other Conditions
Dienogest generally does not appear to affect blood pressure in normotensive women. However, if a sustained clinically significant hypertension develops during the use of dienogest, it is advisable to withdraw dienogest and treat the hypertension.

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

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.

Medical Examination
A complete medical history and physical and gynecological examination should be taken prior to the initiation or reinstitution of dienogest, guided by the contraindications (see **Contraindications**), and should be repeated at least annually during the use of dienogest. The frequency and nature of these assessments should be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs and should also include cervical cytology.

Effects on Ability to Drive and Use Machines
Dienogest has no or negligible influence on the ability to drive and use machines.

INTERACTIONS WITH OTHER MEDICAMENTS
Drug Affecting Hepatic Microsomal Enzymes: Progestogens, including dienogest, are metabolized mainly by the cytochrome P450 system (CYP3A4) located both in the intestinal mucosa and in the liver. Therefore, inducers or inhibitors of CYP3A4 may affect the progestogen drug metabolism.
An increased clearance of sex hormones due to enzyme induction may reduce the therapeutic effect of dienogest and may result in adverse effects e.g., changes in the uterine bleeding profile. A reduced clearance of sex hormones due to enzyme inhibition may increase the exposure to dienogest and may result in adverse effects.
Cytochrome P450 (CYP3A4) Inducers: Interactions may occur with drug substances (e.g., phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, and griseofulvin) that induce CYP3A4 enzymes which may result in increased clearance of sex hormones. Induction of hepatic microsomal enzymes may decrease plasma concentrations of dienogest. 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.
Cytochrome P450 (CYP3A4) Inhibitors: Dienogest is a substrate of CYP3A4. Concomitant administration of strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g., ketoconazole, itraconazole, voriconazole, fluconazole), macrolides (e.g., clarithromycin, erythromycin), diltiazem, and verapamil may increase plasma concentrations of dienogest.
HIV/HCV protease inhibitors (e.g., ritonavir, saquinavir, indinavir, nelfinavir, boceprevir): May increase or decrease plasma concentrations of dienogest. These changes may be clinically relevant in some cases.
Non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine, efavirenz): May result in an increased clearance of dienogest
Antacids (e.g., cimetidine, ranitidine): May increase plasma concentrations of dienogest
Grapefruit juice: May increase plasma concentrations of dienogest St. John's wort (Hypericum perforatum): May induce CYP3A4 enzymes and can result in increased clearance of sex hormones
Other Drugs: 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.
Laboratory Tests: The use of progestogens may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins (e.g., corticosteroid binding globulin and lipid/lipoprotein fractions), parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
Pregnancy: The administration of dienogest during pregnancy is contraindicated. If pregnancy occurs during treatment with dienogest, further intake must be stopped (see **Contraindications**).

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. Animal studies reveal no special risks on pregnancy, embryonic/fetal development, birth, or development after birth for humans.

Dienogest must not be administered to pregnant women because there is no need to treat endometriosis during pregnancy.

Lactation: It is not known if dienogest is excreted in human milk. However, data have shown that dienogest is excreted into milk in rats. Dienogest is contraindicated during breastfeeding (see **Contraindications**).

Elderly: Dienogest is not indicated for use in geriatric (> 65 years of age) patients.

Children: Dienogest is not indicated for use in pediatric patients prior to menarche. The safety and efficacy of dienogest in adolescents (menarche to 18 years of age) have not been established.

UNDESIRABLE EFFECTS
Adverse effects are more common during the first months after the start of treatment with dienogest, and subside with continued treatment. There may be changes in menstrual bleeding pattern, such as spotting, irregular bleeding, or amenorrhea. The most frequently reported adverse effects during treatment with dienogest include headache, breast discomfort, depressed mood, and acne.

Blood and lymphatic system disorders: Anemia
Metabolism and nutrition disorders: Increased appetite, weight decrease, weight increase
Psychiatric disorders: Altered mood, anxiety, depressed mood, depression, insomnia, loss of libido, mood swings, nervousness, sleep disorder
Nervous system disorders: Autonomic nervous system imbalance, disturbance in attention, headache, migraine
Eye disorders: Dry eye
Ear and labyrinth disorders: Tinnitus
Cardiac disorders: Palpitations, unspecific circulatory system disorder
Vascular disorders: Hypotension
Respiratory, thoracic and mediastinal disorders: Dyspnea
Gastrointestinal disorders: Abdominal discomfort, abdominal distension, abdominal pain, constipation, diarrhea, flatulence, gastritis, gastrointestinal inflammation, gingivitis, nausea, vomiting
Skin and subcutaneous tissue disorders: Abnormal hair growth, acne, alopecia, dandruff, dermatitis, dry skin, hirsutism, hyperhidrosis, onychoclasis, photosensitivity reaction, pigmentation disorder, pruritus
Musculoskeletal and connective tissue disorders: Back pain, bone pain, decrease of bone mineral density (particularly in adolescents), heaviness in extremities, muscle spasms, pain in extremity
Renal and urinary disorders: Cystitis, urinary tract infection
Reproductive system and breast disorders: Amenorrhea, atrophic vulvovaginitis, breast discomfort, breast engorgement, breast induration, breast mass, breast pain, fibrocystic breast disease, genital discharge/vaginal discharge, hot flushes, irregularities in menstrual bleeding, ovarian cyst/hemorrhagic ovarian cyst, pelvic pain, uterine/vaginal bleeding including spotting (consists of dysfunctional uterine bleeding, metrorrhagia, menorrhagia, uterine hemorrhage, vaginal hemorrhage), vaginal candidiasis, vulvovaginal dryness including mucosal dryness
General disorders and administration site conditions: Asthenic conditions including asthenia, malaise, edema, face edema, irritability

OVERDOSE AND TREATMENT
A daily intake of 20 to 30 mg dienogest (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.

STORAGE CONDITIONS
Store at temperatures not exceeding 30°C.
Keep the product out of sight and reach of children.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at +632-8-UNILAB-1 (+632-8-864522-1) for Metro Manila or toll-free +1-800-10-UNILAB-1 for provinces, or e-mail productsafety@unilab.com.ph.

By reporting undesirable effects, you can help provide more information on the safety of this medicine.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without a prescription.

AVAILABILITY
Blister Pack x 14's (Box of 28's)

DATE OF REVISION OF THE PACKAGE INSERT: July 2022
DATE OF FIRST AUTHORIZATION: March 2022

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