

ART025073P

DIENOGEST MALAYSIA 2MG 2X14 TABS PIL



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1. NAME OF THE MEDICINAL PRODUCT

Endosafe Tablets 2mg

2. QUALITATIVE AND QUANTITVATIVE COMPOSITION

Each uncoated tablet contains 2mg of dienogest
Excipient: each tablet contains 62.8 mg lactose monohydrate
For excipients, see *List of Excipients*

3. PHARMACEUTICAL FORM

Uncoated tablet.
White to off-white, round, flat faced beveled edge tablets debossed with “NC” on one side and “22” on other side.

4. CLINICAL PARTICULARS

4.1 Indications

Treatment of endometriosis.

4.2 Posology and Administration
Posology

The dosage of Endosafe is one tablet daily without any break, taken preferably at the same time each day with some liquid as needed. The tablet can be taken with or without food. Tablets must be taken continuously without regard to vaginal bleeding. When a pack is finished the next one should be started without interruption. Treatment can be started on any day of the menstrual cycle. Any hormonal contraception needs to be stopped prior to initiation of Endosafe. If contraception is required, non-hormonal methods of contraception should be used (e.g. barrier method).
Management of missed tablets
The efficacy of Endosafe may be reduced in the event of missed tablets, vomiting and/or diarrhea (if occurring within 3-4 hours after tablet taking). In the event of one or more missed tablets, the woman should take one tablet only, as soon as she remembers, and should then continue the next day at her usual time. A tablet not absorbed due to vomiting or diarrhea should likewise be replaced by one tablet.

Additional information on special populations

Paediatric population

Endosafe is not indicated in children prior to menarche. The safety and efficacy of Endosafe was investigated in an uncontrolled clinical trial over 12 months in 111 adolescent women (12 to <18) with clinically suspected or confirmed endometriosis. The use of Endosafe in adolescent patients over a treatment period of 12 months was associated with a mean decrease in Bone Mineral Density (BMD) in the lumbar spine of 1.2%. After cessation of treatment, BMD increased towards pre-treatment levels over a period of 6 months in a subset of patients with decreased BMD (mean change from baseline -0.6%). 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. Therefore the treating physician should weigh the benefits of Endosafe against the possible risks of use in each individual adolescent patient.

Geriatric population

There is no relevant indication for use of Endosafe in the geriatric population.

Patients with hepatic impairment

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

Patients with renal impairment

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

Method of Administration

For oral use.

4.3 Contraindications

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

- 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 tumours (benign or malignant)
- known or suspected sex hormone-dependent malignancies
- undiagnosed vaginal bleeding
- hypersensitivity to the active substance or to any of the excipients listed in Section 6.1

4.4 Warnings and Precautions

As Endosafe is a progestogen-only preparation it can be assumed that the special warnings and precautions for use of progestogen-only preparations are also valid for the use of Endosafe although not all of the warnings and precautions are based on respective findings in the clinical studies with Endosafe. If any of the conditions/risk factors mentioned below is present or deteriorates, an individual risk-benefit analysis should be done before treatment with Endosafe can be started or continued.

Serious uterine bleeding

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

Changes in bleeding pattern

The majority of patients treated with Endosafe experience changes in their menstrual bleeding pattern.

Circulatory disorders

From epidemiological studies there is little evidence for an association between progestogen-only preparations and an increased risk of myocardial infarction or cerebral thromboembolism. Rather, 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 Endosafe (in the case of elective surgery at least four weeks in advance) and not to resume treatment until two 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.

Tumours

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 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. In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of hormonal substances such as the one contained in Endosafe. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking Endosafe.

Osteoporosis

Changes in bone mineral density (BMD)

The use of Endosafe in adolescents (12 to <18 years) over a treatment period of 12 months was associated with a decrease in bone mineral density (BMD) in the lumbar spine (L2-L4). The mean relative change in BMD from baseline to the end of treatment (EOT) was -1.2% with a range between -6% and 5% (IC 95%: -1.70% and -0.78%, n=103). Repeated measurement at 6 months after the 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% (IC 95%: -1.20% and 0.06%, n=60). 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.

In patients who are at an increased risk of osteoporosis a careful risk-benefit assessment should be performed before starting Endosafe because endogenous estrogen levels are moderately decreased during treatment with Endosafe. Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

Other conditions

Patients who have a history of depression should be carefully observed and the drug should be discontinued if the depression recurs to a serious degree. Dienogest generally does not appear to affect blood pressure in normotensive women. However, if a sustained clinically significant hypertension develops during the use of Endosafe, it is advisable to withdraw Endosafe 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 Endosafe. 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 observed while taking Endosafe. 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 whilst taking Endosafe. 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 Endosafe should be decided on 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 Endosafe. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain.

Lactose

Each Endosafe tablet contains 62.8 mg of lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose-free diet should consider the amount contained in Endosafe.

Medical examination

A complete medical history should be taken, and a physical and gynecological examination should be performed prior to the initiation or reinstitution of the use of Endosafe, guided by the contraindications and warnings, and these should be repeated regularly during the use of Endosafe. 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.

4.5 Interactions

Note: The prescribing information of concomitant medication should be consulted to identify potential interactions.

Effects of other medicinal products on Endosafe

Progestogens including dienogest are metabolized mainly by the cytochrome P450 3A4 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 Endosafe and may result in undesirable 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 undesirable effects.

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

e.g. phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John’s wort (Hypericum perforatum).

Enzyme induction can already be observed after a few days of treatment. Maximum enzyme induction is generally seen within a few weeks. After cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

The effect of the CYP 3A4 inducer rifampicin was studied in healthy postmenopausal women. Co-administration of rifampicin with estradiol valerate/dienogest tablets led to significant decreases in steady state concentrations and systemic exposures of dienogest and estradiol. The systemic exposure of dienogest and estradiol at steady state, measured by AUC (0-24h), were decreased by 83% and 44%, respectively.

Substances with variable effects on the clearance of sex hormones:

When co-administered with sex hormones, many combinations of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV inhibitors can increase or decrease plasma concentrations of the progestin. The net effect of 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. The clinical relevance of potential interactions with enzyme inhibitors remains unknown.

Concomitant administration of strong CYP3A4 inhibitors can increase plasma concentrations of dienogest.

Co-administration with the strong CYP3A4 enzyme inhibitor ketoconazole resulted in a 2.9-fold increase of AUC (0-24h) at steady state for dienogest. Concomitant administration of the moderate inhibitor erythromycin increased the AUC (0-24h) of dienogest at steady state by 1.6-fold.

Effects of Endosafe on other medicinal products

Based on in vitro inhibition studies, a clinically relevant interaction of dienogest with the cytochrome P450 enzyme mediated metabolism of other medication is unlikely.

Interaction with food

A standardized high fat meal did not affect the bioavailability of Endosafe.

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.

4.6 Pregnancy, Lactation and Fertility

Pregnancy

There is limited data from the use of dienogest in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

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

Lactation

Treatment with dienogest during lactation is not recommended. It is unknown whether dienogest is excreted in human milk. Data in animals have shown excretion of dienogest in rat milk. A decision must be made whether to discontinue breast-feeding

or to abstain from dienogest therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Based on the available data, ovulation is inhibited in the majority of patients during treatment with dienogest. However, 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 within 2 months after cessation of treatment with dienogest.

4.7 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.

4.8 Undesirable Effects

Undesirable 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 bleeding patterns, such as spotting, irregular bleeding or amenorrhea. The most frequently reported undesirable effects were headache, breast discomfort, depressed mood, and acne. The table below shows the adverse drug reactions (ADRs) of dienogest that are classified according to the system organ.

System organ class	Common	Uncommon
Blood and lymphatic system disorders		Anemia
Metabolism and nutrition disorders	Weight increase	Weight decrease Increased appetite
Psychiatric disorders	Depressed mood Sleep disorder Nervousness Loss of libido Altered mood	Anxiety Depression Mood swings
Nervous system disorders	Headache Migraine	Autonomic nervous system imbalance Disturbance in attention
Eye disorders		Dry eye
Ear and labyrinth disorders		Tinnitus
Cardiac disorders		Unspecific circulatory system disorder Palpitations
Vascular disorders		Hypotension
Respiratory, thoracic and mediastinal disorders		Dyspnoea
Gastrointestinal disorders	Nausea Abdominal pain Flatulence Abdominal distension Vomiting	Diarrhoea Constipation Abdominal discomfort Gastrointestinal inflammation Gingivitis
Skin and subcutaneous tissue disorders	Acne Alopecia	Dry skin Hyperhidrosis Pruritus Hirsutism Onychoclasia Dandruff Dermatitis Abnormal hair growth Photosensitivity reaction Pigmentation disorder
Musculoskeletal and connective tissue disorders	Back pain	Bone pain Muscle spasms Pain in extremity Heaviness in extremities
Renal and urinary disorders		Urinary tract infection
Reproductive system and breast disorders	Breast discomfort Ovarian Cyst Hot flushes Uterine/vaginal bleeding including spotting	Vaginal candidiasis Vulvovaginal dryness Genital discharge Pelvic pain Atrophic vulvovaginitis Breast mass Fibrocystic breast disease Breast induration
General disorders and administration site conditions	Asthenic conditions Irritability	Oedema

Decrease of bone mineral density

In an uncontrolled clinical trial with 111 adolescent women (12 to <18 years) who were treated with dienogest, 103 had BMD measurements. Approximately 72% of these study participants experienced a decrease in BMD of the lumbar spine (L2-L4) after 12 months of use.

4.9 Overdose

Acute toxicity studies performed with dienogest did not indicate a risk of acute adverse effects in case of inadvertent intake of a multiple of the daily therapeutic dose. There is no specific antidote. A daily intake of 20-30 mg dienogest (10 to 15 times higher dose than in Endosafe) over 24 weeks of use was very well tolerated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics

Pharmacotherapeutic group: Progestogens; ATC code: G03DB08

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 oestradiol 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.

Data on efficacy

Superiority of dienogest over placebo was demonstrated in a 3-months study including 198 patients with endometriosis. Endometriosis-associated pelvic pain was measured on a Visual Analog Scale (0-100 mm). After 3 months of treatment with dienogest, a statistically significant difference compared to placebo (Δ = 12.3 mm; 95%CI: 6.4-18.1; $p < 0.0001$) and a clinically meaningful reduction of pain compared to baseline (mean reduction = 27.4 mm $\pm$ 22.9) were demonstrated. After 3 months of treatment, reduction of endometriosis-associated pelvic pain by 50% or more without relevant increase of concomitant pain medication was achieved in 37.3% of patients on dienogest (placebo: 19.8%); a reduction of endometriosis-associated pelvic pain by 75% or more without relevant increase of concomitant pain medication was achieved in 18.6% of patients on dienogest (placebo: 7.3%). The open-label extension to this placebo-controlled study suggested a continued improvement of endometriosis-associated pelvic pain for a treatment duration of up to 15 months.

The placebo-controlled results were supported by the results obtained in a 6 months active-controlled study versus a GnRH agonist including 252 patients with endometriosis. Three studies including a total of 252 patients who received a daily dose of 2 mg dienogest demonstrated a substantial reduction of endometriotic lesions after 6 months of treatment. In a small study (n=8 per dose group), a daily dose of 1 mg dienogest has been shown to induce an anovulatory state after 1 month of treatment. Dienogest has not been tested for contraceptive efficacy in larger studies.

Data on safety

Endogenous estrogen levels are moderately suppressed 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 adult patients before and after 6 months of treatment with dienogest and there was no reduction of mean BMD. In 29 patients treated with leuporelin acetate (LA), a mean reduction of 4.04% $\pm$ 4.84 was noted after the same period (Δ between groups = 4.29%; 95%CI: 1.93-6.66; $p < 0.0003$).

No significant changes of the mean values of standard laboratory parameters (including haematology, blood chemistry, liver enzymes, lipids and HbA1C) were observed during treatment with dienogest for up to 15 months (n=168).

Safety in adolescents

The safety of dienogest with respect to BMD was investigated in an uncontrolled clinical trial over 12 months in adolescent women (12 to <18 years) with clinically suspected or confirmed endometriosis. The mean relative change in BMD of the lumbar spine (L2-L4) from baseline in the 103 patients with BMD measurement was -1.2 %. In a subset of the patients with decreased BMD a follow-up measurement was performed 6 months after end of treatment and showed an increase in BMD to -0.6%.

Long-term safety

A long-term post-approval observational active surveillance study was conducted to investigate the incidence of first-time occurrence or worsening of clinically relevant depression and occurrence of anemia. A total of 27,840 women with a newly prescribed hormonal therapy for endometriosis were enrolled in the study and followed up for up to 7 years. A total of 3,023 women started with a prescription for dienogest 2 mg and 3,371 patients started with other approved endometriosis drugs. The overall adjusted hazard ratio for new occurrences of anemia comparing the dienogest patients with the patients on other approved endometriosis drugs was 1.1 (95%CI: 0.4-2.6). The adjusted hazard ratio for depression risk comparing dienogest and other approved endometriosis drugs was 1.8 (95%CI: 0.3-9.4). A slightly increased risk of depression in dienogest users compared with users of other approved endometriosis drugs could not be excluded.

5.2 Pharmacokinetics

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. Bioavailability is about 91%. The pharmacokinetics of dienogest are dose-proportional within the dose range of 1-8 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 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.

Biotransformation

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.

Elimination

Dienogest serum levels decrease in two phases. The terminal

disposition phase is characterized by a half-life of approximately 9-10 hours. Dienogest is excreted in form of metabolites which are excreted at a urinary to faecal 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.

Steady-state conditions

Pharmacokinetics of dienogest is not influenced by SHBG 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 can be predicted from single dose pharmacokinetics.

Pharmacokinetics in special population

Dienogest has not been studied specifically in renally impaired subjects. Dienogest has not been studied in subjects with hepatic impairment.

5.3 Preclinical safety data

Preclinical data reveal no special risks for humans based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. However, it should be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate (200M) & (30GR), Microcrystalline cellulose (PH101), Potato starch, Crospovidone Type A, Povidone (K-25), Purified water, Talc, Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Please refer to the outer carton

6.4 Storage condition

Store below 30°C
Store in the original package to protect from light and moisture

6.5 Nature and contents of container

Each green PVC/PVDC/Alu blister contains 14 uncoated tablets. Such 2 blisters (2x14 tablets) are packed into an outer cardboard carton along with a package insert.

6.6 Special precautions for disposal

No special requirements

7. MANUFACTURER

Naari Pharma Private Limited
Manufacturing Block-1,
Plot No. 14-16 & 55-57,
Sector-5, IIE, Pantnagar,
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8. PRODUCT REGISTRATION HOLDER

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9. DATE OF REVISION OF THE TEXT

15/11/2024