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

ENDOBREAK

1. Generic Name

Dienogest Tablets 2 mg

2. Qualitative and quantitative composition

Each film-coated tablet contains:

Dienogest IP …….2 mg

Excipients……..q.s.

Colour: Titanium Dioxide I.P.

The excipients used are Microcrystalline Cellulose, Crospovidone, Lactose, Starch, Magnesium Stearate, Talcum, Supercoat and Titanium Dioxide.

3. Dosage form and strength

Dosage form: Film coated tablet

Strength: 2 mg

4. Clinical particulars

4.1 Therapeutic indication

For the management of Pelvic pain associated with Endometriosis

4.2 Posology and method of administration

Dosage: As directed by the Physician.

Method of administration

Dosing Considerations

ENDOBREAK tablets are intended for continuous administration in women for the management of pelvic pain associated with endometriosis. Drug administration can be started on any day of the menstrual cycle.

Special Populations

Renal Impairment

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

Recommended Dose and Dosage Adjustment

The dosage of ENDOBREAK is 1 tablet taken orally every day 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 the next day.

ENDOBREAK may be taken with or without food.

Missed Dose

In the event of a missed tablet, a 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. The efficacy of ENDOBREAK 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). A tablet not absorbed due to vomiting or diarrhea should likewise be replaced by 1 tablet.

Contraindications

ENDOBREAK 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 ENDOBREAK, treatment must be discontinued immediately.

- Known or suspected pregnancy
- Lactation
- Active venous thromboembolic disorder
- Arterial and cardiovascular disease, past or present (eg, 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.

4.4 Special warnings and precautions for use

Warnings

General

Before initiating treatment with ENDOBREAK, pregnancy must be excluded (see **CONTRAINDICATIONS**).

During treatment, patients are advised to use non-hormonal methods of contraception (eg, barrier method) if contraception is required. Hormonal methods of contraception should not be used in combination with ENDOBREAK.

As ENDOBREAK 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 ENDOBREAK although not all of the warnings and precautions are based on respective findings in the clinical studies with ENDOBREAK.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels.

Women should be counselled 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 ENDOBREAK because endogenous estrogen levels are moderately Decreased during treatment with ENDOBREAK. Currently, long-term data on bone mineral density (BMD) and risk of fractures in users of ENDOBREAK are not available. In a reported study BMD was assessed in 21 patients before and after 6 months of treatment with ENDOBREAK 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 ENDOBREAK. Any irregularity or anomaly of the breast should be adequately investigated (eg, 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 ENDOBREAK. 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 ENDOBREAK (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 ENDOBREAK should be discontinued immediately if there is suspicion or symptoms of an arterial or venous thrombotic event (see CONTRAINDICATIONS). ENDOBREAK generally does not appear to affect blood pressure in normotensive women. However, if sustained clinically significant hypertension develops during the use of ENDOBREAK, it is advisable to stop treatment with ENDOBREAK and treat the hypertension.

Hepatic

ENDOBREAK is contraindicated in patients with present or past severe hepatic disease (see **CONTRAINDICATIONS**).

Pancreatic

ENDOBREAK 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 ENDOBREAK.

Psychiatric

Patients who have a history of depression should be carefully observed. ENDOBREAK 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 ENDOBREAK, it is not intended for use as a contraceptive. The menstrual cycle returns to pretreatment characteristics within 2 months after cessation of treatment with ENDOBREAK. If contraception is required, a non-hormonal method (eg, barrier method) should be used. Hormonal methods of contraception should not be used in combination with ENDOBREAK. 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 ENDOBREAK 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 ENDOBREAK. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain.

Changes in Bleeding Pattern

ENDOBREAK treatment affects the menstrual bleeding pattern in the majority of women (see **ADVERSE REACTIONS**).

Uterine bleeding, for example in women with adenomyosis or uterine leiomyomas (fibroids), may be aggravated with the use of ENDOBREAK. If bleeding is heavy and continues over time, this may lead to anemia (severe in some cases). Discontinuation of ENDOBREAK should be considered in such cases. ENDOBREAK 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 pre-treatment characteristics within 2 months after cessation of treatment with ENDOBREAK.

Abnormal vaginal bleeding (eg, 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 ENDOBREAK.

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 ENDOBREAK.

Special Populations

Pregnant Women

The administration of ENDOBREAK during pregnancy is contraindicated

If pregnancy occurs during treatment with ENDOBREAK, 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

ENDOBREAK is contraindicated during lactation (see **CONTRAINDICATIONS**).

It is unknown if dienogest is excreted in human milk. Data in animals have shown excretion in rat milk (see **TOXICOLOGY**).

Geriatrics (> 65 years of age)

ENDOBREAK is not indicated for use in the geriatric population.

Paediatrics (< 18 years of age)

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

4.5 Drugs interactions

Progestogens, including dienogest are metabolised 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 ENDOBREAK 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.

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

The effect of the CYP3A4 inducer rifampicin was studied in healthy postmenopausal women. Co-administration of rifampicin with oestradiol valerate/dienogest tablets led to significant decreases in steady state concentrations and systemic exposures of dienogest. The systemic exposure of dienogest at steady state, measured by AUC (0 – 24h), was decreased by 83%. **Substances with variable effects on the clearance of sex hormones**, (e.g. nevirapine):

When co-administered with sex hormones, many HIV/HCV protease inhibitors (e.g. ritonavir, Saquinavir, indinavir, nelfinavir) and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of the progestogen. 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, fluconazole, and voriconazole), verapamil, macrolides (e.g. erythromycin, clarithromycin), diltiazem, antidepressants (e.g. fluvoxamine, fluoxetine) and grapefruit juice can increase plasma concentrations of the progestogens.

In a reported study investigating the effect of CYP3A4 inhibitors (ketoconazole, erythromycin) on the combination of oestradiol valerate/dienogest, steady state dienogest plasma levels were increased. Co-administration with the strong inhibitor ketoconazole resulted in a 186% increase of AUC (0 – 24h) at steady state for dienogest. When co-administered with the moderate inhibitor erythromycin, the AUC (0 – 24h) of dienogest at steady state was increased by 62%. The clinical relevance of these interactions is unknown.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Geriatrics (> 65 years of age)

ENDOBREAK is not indicated for use in the geriatric population.

Paediatrics (< 18 years of age)

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

Race

No clinically relevant interethnic differences among Caucasian and Japanese patients were observed with respect to the pharmacokinetics and pharmacodynamics of dienogest.

Hepatic Insufficiency

ENDOBREAK is contraindicated in patients with present or past severe hepatic disease

ENDOBREAK has not been studied in patients with impaired liver function.

Renal Insufficiency

ENDOBREAK 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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. No effects on ability to drive and use machines have been observed in users of COCs**.**

4.8 Undesirable effects

Undesirable effects are more common during the first months after start of intake of Endobreak, and subside with duration of treatment (see PRECAUTIONS). The following undesirable effects have been reported in users of Endobreak.

The most frequently reported undesirable effects during treatment that were considered at least possibly related to Endobreak were headache (9.0%), breast discomfort (5.4%), depressed mood (5.1%), and acne (5.1%)

The frequencies of adverse drug reactions (ADRs) by system organ classes reported with dienogest are summarised in Table 1. Within each frequency grouping, undesirable effects are presented in order of decreasing frequency. Frequencies are defined as common (≥1/100 to <1/10) and uncommon (≥1/1000 to <1/100). The frequencies are based on pooled data of four clinical trials including 332 patients (100.0%).

Table 1: Categorised relative frequency of women with ADRs, by SOC, 2 mg dienogest group – based on reported pooled data of four clinical trials including 332 patients

System Organ Class	Common	Uncommon	Rare
Blood and lymphatic system disorders		**Anaemia (1; 0.3%)**	
Metabolism and nutrition disorders	Weight increased (12; 3.6 %)	Weight decreased (1; 0.3%) Increased appetite (1; 0.3%)	
Psychiatric disorders	Depressed mood (17; 5.1%) Sleep disorder1 (7; 2.1%) Nervousness (5; 1.5%) Loss of libido (5; 1.5%) Mood altered (4; 1.2%)	Anxiety (2; 0.6%) Depression (2; 0.6%) Mood swings (1; 0.3%)	
Nervous system disorders	Headache (30; 9.0%) Migraine (4; 1.2%)	Autonomic nervous system imbalance (3; 0.9%) Disturbance in attention (2; 0.6%	
Eye disorders		Dry eye (1; 0.3%)	

Ear and labyrinth disorders		Tinnitus (1; 0.3%)	
Cardiac disorders		Unspecified circulatory system disorder (1; 0.3%) Palpitations (1; 0.3%)	
Vascular disorders		Hypotension (1; 0.3%)	
Gastrointestinal disorders	Nausea (14; 4.2%) Abdominal painII (12; 3.6%) Flatulence (10; 3.0%) Abdominal distension (4; 1.2%) Vomiting (4; 1.2%)	Diarrhoea (2; 0.6%) Constipation (2; 0.6%) Abdominal discomfort (2; 0.6 %) Gastrointestinal inflammationIII (2; 0.6%) Gingivitis (1; 0.3%)	
Respiratory, thoracic and mediastinal disorders		Dyspnoea (1; 0.3%)	
Skin and subcutaneous tissue disorders	Acne (17; 5.1%) Alopecia (5; 1.5%)	Dry skin (3; 0.9%) Hyperhidrosis (2; 0.6%) Pruritus (2; 0.6%) Hirsutism (1; 0.3%) Onychoclasis (1; 0.3%) Dandruff (1; 0.3%) Dermatitis (1; 0.3%) Hair growth abnormal (1; 0.3%) Photosensitivity reaction (1; 0.3%)	

		Pigmentation disorder (1; 0.3%)	
Musculoskeletal and connective tissue disorders	Back pain (4; 1.2%)	Bone pain (1; 0.3%) Muscle spasms (1; 0.3%) Pain in extremity (1; 0.3%) Heaviness in extremities (1; 0.3%)	
Renal and urinary disorders			Urinary tract infection IV (2; 0.6%)
Reproductive system and breast disorders	Breast discomfort V (18; 5.4%) Ovarian cyst VI (10; 3.0%) Hot flush (9; 2.7%) Uterine / Vaginal bleeding including Spotting VII ,VIII (5; 1.5%)	Vaginal candidiasis (3; 0.9%) Vulvovaginal dryness IX (3; 0.9%) Genital discharge X (2; 0.6%) Pelvic pain (2; 0.6%) Atrophic vulvovaginitis (1; 0.3%) Breast mass (1; 0.3%) Fibrocystic breast disease (1; 0.3%) Breast induration (1; 0.3%)	
General disorders and administration site conditions	Asthenic conditions XI (10; 3.0%) Irritability (5; 1.5%) Irritability (5; 1.5%)		Oedema XII (2; 0.6%)

Most appropriate MedDRA term (version 11.0) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

I Sleep disorder consists of sleep disorder (5; 1.5%), insomnia (2; 0.6%).

II Abdominal pain consists of abdominal pain (5; 1.5%), abdominal pain lower (5; 1.5 %), abdominal pain upper (2; 0.6%).

III Gastrointestinal inflammation consists of gastrointestinal inflammation (1; 0.3%), gastritis (1; 0.3%).

IV Urinary tract infection consists of urinary tract infection (1; 0.3%), cystitis (1; 0.3%)

V Breast discomfort consists of breast discomfort (11; 3.3%), breast engorgement (4; 1.2%), and breast pain (3; 0.9%).

VI Ovarian cyst consists of ovarian cyst (9; 2.7%), haemorrhagic ovarian cyst (1; 0.3 %).

VII Uterine/ Vaginal bleeding including spotting consists of dysfunctional uterine bleeding (1; 0.3%), Metrorrhagia (1; 0.3%), menorrhagia (1; 0.3%), uterine haemorrhage (1; 0.3%), vaginal haemorrhage (1; 0.3%).

VIII According to bleeding diaries, irregularities in menstrual bleeding occurred more often but were usually not reported as adverse drug reaction by the patients. Please refer to text below the table for further information.

IX Vulvovaginal dryness consists of vulvovaginal dryness (2; 0.6%), mucosal dryness (1; 0.3%).

X Genital discharge consists of genital discharge (1; 0.3%) and vaginal discharge (1; 0.3%).

XI Asthenic conditions consists of fatigue (6; 1.8%), asthenia (2; 0.6%), and malaise (2; 0.6 %).

XII Oedema consists of oedema (1; 0.3%), face oedema (1; 0.3%).

Uterine bleeding irregularities

Menstrual bleeding patterns were assessed systematically using patient diaries and were analysed using the WHO 90 day reference period method. During the first reference period (i.e. first 90 days of treatment with Endobreak): 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 previous categories (19.7%)‡.

During the fourth reference 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 previous categories (22.8%) ‡.

Changes in menstrual bleeding patterns were only occasionally reported as adverse event by the patients (see Table 1).

4.9 Overdose

A reported clinical study has shown that 20 to 30 mg dienogest per day (10 to 15 times the recommended dose of ENDOBREAK) over 24 weeks of use in women was generally well tolerated. (9) There is no specific antidote to a ENDOBREAK overdose and further treatment should be symptomatic, based on the pharmacological action of dienogest.

5. Pharmacological properties

5.1 Mechanism of Action

Dienogest is a novel nortestosterone derivative with no androgenic but rather an antiandrogenic activity of approximately one third 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.

5.2 Pharmacodynamic properties

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 in 20 healthy women, a daily dose of 2 mg dienogest has been shown to induce an ovulatory state after 1 month of treatment. ENDOBREAK has not been tested for contraceptive efficacy. ENDOBREAK is not intended for use as a contraceptive. If contraception is required, a no hormonal method should be used (see **WARNINGS AND PRECAUTIONS**).

Endogenous estrogen levels are only moderately suppressed during treatment with ENDOBREAK.

Based on available data, the menstrual cycle returns to pretreatment characteristics within 2 months after cessation of treatment with ENDOBREAK.

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. ENDOBREAK does not increase the incidence or intensity of hot flushes.

5.3 Pharmacokinetic properties

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 ENDOBREAK 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). Ten percent (10%) of the total serum drug concentrations are present as free steroid; 90% are non-specifically 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.

Special Populations and Conditions

Geriatrics (> 65 years of age)

ENDOBREAK is not indicated for use in the geriatric population.

Pediatrics (< 18 years of age)

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

Race

No clinically relevant interethnic differences among Caucasian and Japanese patients were observed with respect to the pharmacokinetics and pharmacodynamics of dienogest.

Hepatic Insufficiency

ENDOBREAK is contraindicated in patients with present or past severe hepatic disease (see also **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**). ENDOBREAK has not been studied in patients with impaired liver function.

Renal Insufficiency

ENDOBREAK 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.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Acute Toxicity

Reported single-dose toxicity studies were conducted in several species including mice, rabbits, rats, and dogs. All of the studies revealed a very low toxicity of dienogest after single oral or parenteral administration. Nonlethal doses were between 1000 and 4000 mg/kg with the exception of male rabbits where it was below but close to 1000 mg/kg. Toxic signs observed at high doses were central depression in mice, none in rats, anorexia, weight loss, convulsions in rabbits, and a transient increase in GPT in dogs without histopathological findings.

Repeated-Dose Toxicity

Reported repeated-dose systemic toxicology studies of dienogest were conducted for various durations up to 13 weeks in mice, 12 months in rats, 6 months in dogs, and up to 12 months in monkeys.

In general, the principle findings observed in all studies were pharmacological or exaggerated pharmacological effects associated with the repeated administration of high dose levels of a progestogenic compound to laboratory animals.

In mice, dienogest was well tolerated when given orally at dose levels up to 125 mg/kg/day for 13 weeks. Principle changes were pharmacological in nature (lower uterus and cervix weights at dose levels of 25 mg/kg/day and higher ovary and lower seminal vesicle weights at dose levels of 125 mg/kg/day). At the high-dose level (125 mg/kg/day), increased absolute and relative liver weights were observed in male and female mice and were accompanied by periacinar hepatocyte hypertrophy in males. When given at a dose of 60 mg/kg to female mice, a depression of body weight gain and of haematopoiesis were the major additional findings. Toxicokinetic studies in mice were performed first in a separate 5-day study as well as in the 13-week study after the 60 mg/kg dose and later during the carcinogenicity study in this species. Up to an 18-fold multiple of human exposure to dienogest was studied in this species in terms of AUC (0-24h).

Reported repeated-dose systemic toxicology studies were conducted in female rats for 3, 6, and 12 months. In these studies, dienogest was well tolerated and not lethal when orally administered daily for 3 months at dose levels up to 30 mg/kg or for 6 and 12 months at doses up to 10 mg/kg/day. In the 3-month study, 3.0 mg/kg/day was identified as the NOAEL. In the 12-month study, 1.0 mg/kg/day was identified as the NOAEL. Body weights were unaffected in the 3-month study in animals given doses as high as 30 mg/kg/day, but were 9% and 12% higher than controls after daily oral administration of 0.1 and 1.0 mg/kg/day, respectively, for 12 months. Compared with controls, changes observed across the rat studies were predominantly pharmacological in nature and included persistent diestrus (30 mg/kg/day), lower average serum total cholesterol ($\geq$ 3 mg/kg) and alanine and/or aspartate aminotransferase values ($\geq$ 10 mg/kg/day), slightly higher serum triglyceride and nonesterified fatty acid values ($\geq$ 0.1 mg/kg/day), alterations in coagulation parameters (higher platelet counts, fibrinogen values or longer prothrombin times after administration of doses $\geq$ 10 mg/kg), higher absolute and relative liver weights ($\geq$ 1.0 mg/kg/day), and microscopic changes in target organs (ovaries, uterus and vagina) at most dose levels $\geq$ 1.0 mg/kg/day. Slightly lower erythrocytic parameters (typically erythrocyte counts, hemoglobin, and hematocrit), compared with controls were also observed in some of the studies. Microscopic liver changes including basophilic foci of cellular alteration, periportal fat deposition, and vacuolated hepatocytes were observed after oral administration of 10 mg/kg/day for 12 months. The liver changes seen only in this chronic study most likely reflect earlier onset of age-related changes in female rats, and

similar findings have been described after high dose levels of progestins were administered in chronic toxicity studies in rodents. Toxicokinetic investigations showed that up to a 29-fold multiple of human exposure to dienogest was achieved in the 3-month studies in female rats and a 12-fold exposure was achieved in the pivotal 1-year study in terms of multiples of AUC(0-24h). In another reported non-GLP, supportive study, dienogest or levonorgestrel was administered to rabbits in their daily diet for 19 to 20 months at concentrations intended to deliver 0.14 or 0.70 mg/day. No intrinsic organ toxicity was observed following dietary administration of dienogest or levonorgestrel. In general, changes observed were limited to pharmacologic or exaggerated pharmacologic effects of progestins.

Dienogest was orally administered to female Beagle dogs in 3 reported studies. In the first supportive study, dienogest was administered as powder in gelatin capsules once daily for 1 month at doses of 0.1 to 10 mg/kg/day. In the second study, dienogest, as a liquid suspension in gelatin capsules, was administered once daily for 3 months at doses of 0.3 to 3.0 mg/kg/day. In a second supportive study, dienogest was administered as coated tablets once daily for 6 months at doses of 0.01 to 1 mg/kg/day. In general, dienogest was well tolerated and nonlethal. Pharmacological changes observed in the female dogs included slight increases in body weight, enlargement of the mammary gland accompanied microscopically by lobular hyperplasia, and histopathological changes in the ovaries, vagina, pituitary, and uterus. Clinical pathology changes included lower-than-control erythrocytic parameters (erythrocyte counts, hemoglobin, hematocrit) which were sometimes accompanied by alterations in lipid parameters and/or alterations in coagulation parameters. Sulfobromophthalein (BSP)-retention showed a slight, dose-dependent increase under dienogest in female animals at the mid- and high-dose level which was prominent in 1 animal in the second BSP test performed during the study. However, there was no morphological correlate in the liver of this dog.

In a reported study Dienogest was orally administered to female Cynomolgus monkeys, once daily for 13 weeks at dose levels of 0.4, 2.0, and 10.0 mg/kg. Drug-induced cessation of menses occurred at all dose levels. No signs of intolerance or organ toxicity were observed at any dose level tested. AUC(0-24h) values for the high dose (10 mg/kg) in this GLP compliant study were ca 118 times higher than systemic exposure in women administered repeated 2 mg doses of dienogest. In repeated-dose studies in female Rhesus monkeys, dienogest was orally (intragastrically) administered at dose levels of 0.1, 1, and 10 mg/kg/day for 3 or 12 months. An additional dose level of 0.3 mg/kg/day was also evaluated in the 12-month study. No compound-related mortality, effects on body weight, food consumption, ECG, ophthalmology, or urinalysis parameters were observed in either study. The NOAEL was identified as 1 mg/kg/day.

Pharmacological effects, such as cessation of menstruation (all dose levels, and shown to be reversible in the 3-month study), serum biochemistry changes (lower than control alkaline phosphatase values after administration of 10 mg/kg/day), alterations in coagulation parameters (such as increases in fibrinogen and plasminogen activity but without effect on coagulation times or thromboelastograms), and intimal thickening and hypertrophy of the uterus were observed in each study. Furthermore, apart from a 2-fold increase in GPT in a single high-dose monkey and only in week 4 (as compared to the mean in controls) of the 3-month study, there was no indication of liver toxicity in any of the 3 monkey studies. The highest dose of 10 mg/kg in the pivotal 1-year monkey study resulted in 75 times the human dienogest exposure Carcinogenicity Slightly increased incidences of malignant lymphomas and pituitary adenomas were seen in malemice during a 2-year carcinogenicity study. Female mice showed an increased incidence of uterine stromal polyps at the highest tested dose level. These findings are considered to be related to the weak estrogenic partial activity of dienogest in rodents. In 1 of the 2 rat carcinogenicity studies, there was an increased incidence of pituitary

adenomas and fibro epithelial tumors of the mammary gland in male animals. There was no change in tumour incidence in female rats in both studies. These observations do not suggest particular human risks apart from those which are generally assumed for the use of progestogenic compounds. In vitro studies have shown varied and dose-dependent effects of progestins, including dienogest, on the proliferation of primary human breast cancer cell lines (HCC1500 and MCF-7). These effects appear to differ from those of progesterone. Dienogest alone has not been shown to stimulate cell proliferation in normal breast cell lines (MCF10A), but it demonstrated a minor stimulatory effect on malignant estrogen-receptor positive breast cells (HCC1500). While in vitro findings cannot be extrapolated to in vivo or clinical situations, dienogest is a novel progestin with a distinct pharmacological profile compared to progesterone or other progestins.

Reproductive Toxicology

Reported reproductive toxicity studies with dienogest gave no indication of a teratogenic potential up to embryo lethal doses. The inhibition of implantation in rats might be due to an estrogenic effect and the impairment of tubal transport of ova and the postimplantational losses further indicate a disturbance of the endocrine milieu. The fertility of female offspring was impaired after high doses of dienogest given during late pregnancy and lactation. Taken together, the results of reproductive toxicity testing with dienogest do not differentiate this drug from other progestins.

Mutagenesis

In a reported study two reverse mutation tests in bacteria (Ames test) were conducted. In both tests, dienogest was negative up to a dose of 5 mg per plate. Furthermore, dienogest in concentrations up to a cytotoxic dose of 500 µg/mL (with and without metabolic activation) did not induce mutations in the TK locus in L5178Y mouse lymphoma cells.

Dienogest also did not induce chromosomal aberrations in Chinese hamster lung cells in culture up to a cytotoxic dose of 110 µg/mL (without metabolic activation) and 220 µg/mL (with metabolic activation). In a chromosomal aberration test in human lymphocytes, dienogest was negative. Oral doses up to 2 g/kg did not induce micronuclei of polychromatic erythrocytes in the bone marrow of female mice above the control level in 2 studies. In a rat liver initiation-promotion model in vivo, dienogest did not induce paraneoplastic enzyme-altered foci up to a dose of 140 mg/kg for 5 consecutive days followed by treatment with clophen A50 over 11 weeks. In the same test, diethyl nitrosamine was clearly positive.

Dienogest did not induce chromosomal aberrations in the bone marrow cells of pregnant baboons or in the lymphocytes of their newborn up to a dose of 1.6 mg dienogest. A dose of 100 mg/kg dienogest injected intraperitoneally to mice slightly suppressed the incorporation of radioactively labeled thymidine into DNA of the kidney and somewhat more of the liver. However, the difference was not significant at the specified significance limit of 1%.

Other negative tests briefly reported by Schöneich et al included the rec-type repair test with *Proteus mirabilis*, another Ames test, a host-mediated assay with *Salmonella typhimurium* in the rat, the cytogenetic assays with ascites tumour or bone-marrow cells in mice, and a dominant lethal test with male and female mice. In all tests performed (which exceeded the extent requested by international guidelines), dienogest showed no mutagenic potential.

Additionally, a UDS (unscheduled DNA synthesis) test was conducted in primary hepatocytes of female rats in vitro. Two independent experiments were performed in which freshly isolated hepatocytes were exposed to dienogest for 18 hours in the presence of methyl-3H-thymidine. The uptake of radioactivity was determined by autoradiography. In the first series of experiments, a significant increase in net grains was found with 2 AAF and 10 or 15 µg/mL

CMA, but also with the dienogest concentrations evaluated between 1.72 and 220 µg/mL. In the second experiment, 2 AAF was positive, but to a much lesser degree, and dienogest was only positive at the highest concentration of 220 µg/mL, which was slightly cytotoxic. Dienogest showed a weak genotoxic potential only in this UDS test of the female rat. In a second UDS test in male rat hepatocytes, dienogest did not induce UDS at concentrations up to a cytotoxic dose of 250 µg/mL in either of two independent experiments.

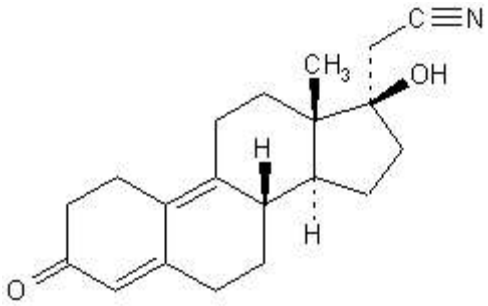
According reported data, to support the evaluation of the above-mentioned UDS results in female rat hepatocytes, an in vivo/in vitro UDS assay in female rats was performed. Dienogest was given orally at extremely high dosages of 2000 mg/kg and 200 mg/kg. The animals were anesthetized and sacrificed by enzymatic liver perfusion 2 and 16 hours after dosing. Primary hepatocyte cultures were established and exposed for 4 hours to methyl-3H-thymidine. The maximal dose of 2000 mg/kg bw corresponds to 60,000-fold of the daily human dienogest dose. Dienogest was considered no effective in inducing DNA damage, leading to increased repair synthesis in this in vivo/in vitro UDS assay.

In a reported study Dienogest was tested for its potential to generate DNA adducts in human liver slices after in vitro incubation over 6 hours. After incubation with dienogest or spironolactone, DNA-adduct level were below or at the level of quantification. No DNA-adducts were observed in any female livers after incubation with dienogest up to concentrations of 5000 ng/mL. In 2 of 3 male livers no adducts were found and in only one liver a very low DNA adduct level (3.94/109 nucleotides) at the limit of quantification was found at an extremely high dienogest concentration of 5000 ng/mL. It was concluded that dienogest did not produce DNA-adducts in human liver slices to a relevant degree.

7. Description

Dienogest is 2-[(8S, 13S, 14S, 17R)-17-hydroxy-13-methyl-3-oxo-1,2,6,7,8,11,12,14,15,16-decahydrocyclopentaphenanthren-17-yl]acetonitrile.

The molecular weight is 311.4 and empirical formula is $C_{20}H_{25}NO_2$. The chemical structure is as below:



Dienogest is off-white to slightly yellow powder. It is slightly soluble in dichloromethane and practically insoluble in water.

Dienogest Tablets are White coloured, round, biconvex, film coated tablets, plain on both sides. The excipients used are Microcrystalline Cellulose, Crospovidone, Lactose, Starch, Magnesium Stearate, Talcum, Supercoat and Titanium Dioxide.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

Endobreak is packed in blister strips of 10 tablets.

8.4 Storage and handing instructions

Store at a temperature not exceeding 25^0C in a dry & dark place. Keep out of reach of children.

9. Patient Counselling Information

Read all of this leaflet carefully before you start taking this medicine.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

• If any of the side effects gets troublesome or serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet.

9.1.What ENDOBREAK is and what it is used for

9.2.What you need to know before you take ENDOBREAK

9.3.How to take ENDOBREAK

9.4.Possible side effects

9.5.How to store ENDOBREAK

9.6.Contents of the pack and other information

9.1 What ENDOBREAK is and what it is used for

ENDOBREAK is a treatment for the painful symptoms caused by endometriosis in women who are 18 years of age and older and have had the first menstrual cycle (menarche).

ENDOBREAK works to help reduce pelvic pain associated with endometriosis (endometrium-like tissues outside the uterus which cause a chronic inflammation).

9.2 What you need to know before you take Endobreak

You should not use ENDOBREAK if you:

- are pregnant
- are breastfeeding
- Are suffering from a medical condition related to a blood clot (thromboembolic disorder). This may occur, for example, in the blood vessels of the legs (deep vein thrombosis) or the lungs (pulmonary embolism).
- have or have ever had a disease affecting the arteries, including cardiovascular disease, such as a heart attack, stroke, or heart disease which causes a reduced blood supply (angina pectoris)
- have diabetes with blood vessel damage

- Have or have ever had severe liver disease (and your liver function values have not returned to normal). Symptoms of liver disease may be yellowing of the skin and/or itching of the whole body.
- have or have ever had a benign or malignant liver tumor
  - Have ever suffered from a malignant tumor such as cancer of the breast or the reproductive organs".
  - have any unexplained vaginal bleeding
  - loss of vision due to blood vessel disease of the eye
  - migraine headache
  - are allergic to dienogest or any of the other ingredients of ENDOBREAK (see What the medicinal ingredient is and What the nonmedicinal ingredients are) If any of these conditions appear for the first time while you are using ENDOBREAK , stop taking it at once and consult your doctor. When not to take Endobreak. You should not use Endobreak if you have any of the conditions listed below. If you do have any of the conditions listed below, you must tell your doctor. Your doctor will discuss with you what other form of birth control would be more appropriate.
  - **WARNINGS AND PRECAUTIONS**

    Before starting ENDOBREAK, you must be sure that you are not pregnant and must stop taking any form of birth control that contains hormones such as the pill, patch, intrauterine system, injection, or ring.

    While using ENDOBREAK you must use a nonhormonal birth control method such as condoms or a diaphragm. DO NOT use any form of birth control that contains hormones.

    ENDOBREAK is not a birth control method and will not prevent pregnancy. Safety and efficacy of ENDOBREAK in women under 18 years of age has not been established.

    Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. You should not smoke while taking ENDOBREAK.

    BEFORE you use ENDOBREAK, talk to your doctor or pharmacist if you:

- have ever had a medical condition related to a blood clot (thromboembolic disorder) or anyone in your family has had a blood clot at a relatively early age mediate has had a blood clot at a relatively early age.
- have a close relative who has had breast cancer
- suffer or have suffered from depression
- have uncontrolled high blood pressure
- Have a history of liver disease. Symptoms may include yellowing of the skin or eyes or itching all over your body. Inform your doctor also if such symptoms occurred during a previous pregnancy.
- have diabetes or had diabetes temporarily during a previous pregnancy
- have ever had chloasma (golden-brown patches on the skin, particularly on the face)

  The Risks of Using ENDOBREAK

1. Circulatory Disorder (including blood clots in the legs, lungs, heart, eyes, or brain) some studies have suggested that women who use progestin only medications might have a slightly higher risk of blood clots; however, the results are not certain. You should discuss risk factors for blood clots with your doctor. Be alert for the following symptoms and signs of serious adverse effects associated with blood clots. Call your doctor immediately if they occur:

- Sharp pain in the chest, coughing blood, or sudden shortness of breath.
- Pain and/or swelling in the calf.
- Crushing chest pain or heaviness.
- Sudden, severe, or worsening headache or vomiting, dizziness or fainting, disturbances of vision or speech, or weakness or numbness in an arm or leg.
- Sudden partial or complete loss of vision.

2. Breast Cancer

The most significant risk factors for breast cancer are increasing age and a strong history of breast cancer in the family (mother or sister). Other established risk factors include onset of menstrual periods before age 12 years, never having children, having your first full-term pregnancy after the age of 30 years, never having breastfed a child, and daily alcohol consumption. Some studies have shown that the risk of developing breast cancer does not appear to be increased by using progestin-only therapies like ENDOBREAK. However, more thorough studies are needed to confirm that there is no increased risk. You should also discuss breast self-examination with your doctor and report any breast lumps. A yearly breast examination by a health care professional is recommended for all women.

3. Diabetes

Patients with diabetes who use ENDOBREAK should have their blood glucose levels closely monitored.

4. Ectopic Pregnancy

If you become pregnant while taking ENDOBREAK, you are at a slightly increased risk of having an ectopic pregnancy (the embryo develops outside the womb). Before you start taking ENDOBREAK, tell your doctor if you had an ectopic pregnancy in the past or have an impaired function of the fallopian tubes.

5. Liver Tumors

In rare cases, benign liver tumors, and in even fewer cases malignant liver tumors, have been reported in women taking hormones. Contact your doctor if you have unusually severe stomach pain.

Other medicines and Endobreak

Some medicines may interact with ENDOBREAK. Let your healthcare professional know what other medicines you are taking.

Drugs that may interact with ENDOBREAK include:

- Antifungals (eg, ketoconazole, itraconazole, fluconazole, voriconazole),
- Antibiotics (eg, erythromycin, clarithromycin, rifampicin)
- Antidepressants (eg, fluvoxamine, fluoxetine)

- Anticonvulsants (eg, phenytoin, primidone, carbamazepine)
- Antacids (eg, cimetidine, ranitidine)
- Blood pressure medication (eg, diltiazem, verapamil)
- Drugs used for the treatment of HIV/Hepatitis C Virus infections (eg, ritonavir, Saquinavir, indinavir, nelfinavir, boceprevir) Herbal or food products that may interact with ENDOBREAK include:
- St. John's wort
- Grapefruit juice

See also **ABOUT THIS MEDICATION**: When it should not be used, and **SIDE EFFECTS AND WHAT TO DO ABOUT THEM.**

9.3 How to take Endobreak

Dose: As directed by physician.

Overdose

In cases of drug overdose talk to your doctor, or a poison control centre, or go to the emergency room of a hospital near you.

Missed Dose

ENDOBREAK will be less effective if you miss a tablet or have vomiting or diarrhea. If you miss one or more tablets or in case of vomiting or diarrhea within 3-4 hours of taking a tablet, take a tablet as soon as you remember and then continue taking the tablet the next day at your usual time. Do not take more than one tablet per day.

9.4 **Possible side effects**

Like all medicines, ENDOBREAK can cause side effects. These effects are more common during the first months after you start ENDOBREAK and usually disappear or lessen with continued use. You may also experience changes in your menstrual bleeding pattern, such as spotting, irregular bleeding, or your periods may stop completely. You should consult your physician if your periods become longer or heavier.

Common side effects (between 1 and 10 in every 100 users may be affected):

- weight gain
- depressed mood, problems sleeping, nervousness, or loss of interest in sex
- headache or migraine
- nausea or abdominal pain
- acne or hair loss
- breast discomfort
- ovarian cyst
- uterine/vaginal bleeding including spotting
- generalized weakness
- irritability

Uncommon side effects (between 1 and 10 in every 1,000 users may be affected):

- increase in appetite
- anxiety, depression, changed mood, or mood swings
- disturbed attention
- dry eyes
- ringing in the ears
- palpitations

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

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

9.5.HOW TO STORE ENDOBREAK

Store at a temperature not exceeding 25^0C in a dry & dark place. Keep all medicines out of reach of children.

9.6. Contents of the pack and other information

What Endobreak contains

The active substances is dienogest.

The excipients used are Microcrystalline Cellulose, Crospovidone, Lactose, Starch, Magnesium Stearate, Talcum, Supercoat and Titanium Dioxide.

10. Details of manufacturer

Manufactured by:

Synokem Pharmaceuticals Ltd.

Plot No. 56-57, Sector 6A, I.I.E, SIDCUL,

Ranipur (BHEL) Hardiwar – 249403, Uttarakhand.

11. Details of permission or licence number with date

Mfg Lic No 27/UA/SC/P-2018 issued on 22.11.2018

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ ENDOBREAK 2mg /AUG-2020/01/PI