CIPGEST Tablets (Dienogest)

For the Use of a Registered Medical Practitioner only

Qualitative and Quantitative Composition

Each film coated tablet contains:

Dienogest IP … 2 mg

Excipients … q.s.

Dosage Form and Strength

2 mg tablets for oral use.

Clinical Particulars

Therapeutic Indications

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

Posology and Method of Administration

The dosage of **CIPGEST** is one tablet daily without any break, taken orally, preferably at the same time each day with some liquid as needed. The tablet can be taken with or without food. **CIPGEST** must be taken continuously without regard to vaginal bleeding. When a pack is finished, the next one should be started without interruption. There is no experience with dienogest treatment for >15 months in patients with endometriosis. Treatment can be started on any day of the menstrual cycle.

Any hormonal contraception needs to be stopped prior to initiation of **CIPGEST**. If contraception is required, non-hormonal methods of contraception should be used (e.g. barrier method).

If a short-acting (e.g. oral) hormonal treatment was prescribed before starting treatment with dienogest, treatment may be started on the first day of menstrual bleeding after cessation of treatment.

If a long-acting (i.e. injectable) hormonal treatment was administered before starting treatment with dienogest, then dienogest may be started once metabolism/excretion of the previously administered drug is expected to be completed.

Management of Missed Tablets

The efficacy of **CIPGEST** may be reduced in the event of missed tablets, vomiting and/or diarrhoea (if occurring within 3-4 hours after tablet taking). In the event of 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 diarrhoea should likewise be

replaced by one tablet.

Contraindications

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

- Known or suspected pregnancy
- Lactation
- Active venous thromboembolic disorder

- Arterial and cardiovascular disease, past or present (e.g. myocardial infarction, cerebrovascular accident, ischaemic 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
- 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 the active substance or to any of the excipients

Special Warnings and Precautions for Use

General

Before starting dienogest treatment, pregnancy must be excluded. During treatment, patients are advised to use non-hormonal methods of contraception (e.g. barrier contraception such as condom) to prevent unwanted pregnancies.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. Women should be counselled not to smoke.

As dienogest 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 dienogest although not all the warnings and precautions are based on respective findings in the clinical studies with dienogest. If any of the conditions/risk factors mentioned below are present or deteriorate, an individual risk-benefit analysis should be done before treatment with dienogest can be started or continued.

Changes in Bleeding Pattern

The majority of patients treated with dienogest experience changes in their menstrual bleeding pattern. Dienogest is expected to exhibit typical progestogenic effects on the endometrium by reducing oestrogen 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 dienogest. Abnormal vaginal bleeding (e.g. prolonged and/or heavy) should be thoroughly investigated by pelvic ultrasound, endometrial biopsy or hysteroscopy.

Serious Uterine Bleeding

Uterine bleeding, e.g. 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 anaemia (severe in some cases). In the event of anaemia, discontinuation of dienogest should be considered.

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 ([VTE]; deep venous thrombosis, pulmonary embolism) associated with the use of progestogen-only preparations. Generally recognized risk factors for 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 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 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 oestrogen-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).

In rare cases, benign liver tumours and, even more rarely, malignant liver tumours have been reported in users of hormonal substances such as dienogest. 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 dienogest.

Osteoporosis/Changes in Bone Mineral Density (BMD)

In patients who are at an increased risk of osteoporosis, a careful risk-benefit assessment should be performed before starting dienogest because endogenous oestrogen levels are moderately decreased during treatment with dienogest. Currently, long-term data on 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 leuprorelin acetate, a mean reduction of 4.04% ± 4.84 was noted after the same period (difference between groups = 4.29%; 95%CI: 1.93-6.66; p<0.0003).

The safety and efficacy of dienogest was investigated in 111 adolescent women (12 to <18 years of age) with clinically suspected or confirmed endometriosis in an uncontrolled clinical trial over 12 months. The use of dienogest in adolescent patients over a treatment period of 12 months was associated with a mean decrease in BMD in the lumbar spine (L2-L4) of 1.2% in 103 patients. 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 dienogest against the possible risks of use in each individual adolescent patient also taking into account the presence of significant risk factors for osteoporosis (e.g. metabolic bone disease, family history of osteoporosis, low body mass index or eating disorders such as anorexia nervosa or bulimia, chronic use of medicines that can reduce bone mass, e.g. anticonvulsants or corticosteroids, previous low trauma fracture, alcohol abuse and/or smoking).

If clinically warranted, BMD may be monitored and the results used in the risk-benefit assessment of use of dienogest.

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

Sexual Function/Reproduction

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. Hormonal methods of contraception should not be used in combination with dienogest. The menstrual cycle returns to pre-treatment characteristics within 2 months after cessation of treatment with dienogest.

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 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 dienogest. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain.

Other Conditions

Patients who have a history of depression should be carefully observed and the drug should be discontinued if clinically relevant depression occurs or if pre-existing depression is aggravated to a

serious degree during treatment.

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 that occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of dienogest.

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 dienogest.

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

Medical Examination

A complete medical history and physical and gynaecological examination should be taken prior to the initiation or reinstitution of dienogest, 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.

Laboratory Tests

The use of progestogens may influence the results of certain laboratory tests (e.g. gonadotropin, endogenous hormones).

The results of certain endocrine and liver function tests may be affected by progestin-containing products, 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 coagulation, fibrinolysis and carbohydrate metabolism (impaired glucose tolerance), and reduced serum folate concentration. Changes generally remain within the normal laboratory range.

However, no significant impact on standard laboratory parameters, including haematology, blood chemistry, liver enzymes, lipids and HbA1C, was observed during treatment with dienogest for up to 15 months (n=168).

Drug Interactions

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

Dienogest should not be prescribed simultaneously with other steroids, including danazol.

Effects of Other Medicinal Products on Dienogest

Individual Enzyme Inducers or Inhibitors (CYP3A4)

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 dienogest 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, nevirapine and products containing St. John's wort (*Hypericum perforatum*) that induce microsomal enzymes (e.g. CYP450 enzymes).

Enzyme induction can already be observed after a few days of treatment. Maximum enzyme induction is generally seen within a few (2-3) weeks. After cessation of drug 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 and oestradiol. The systemic exposure of dienogest and oestradiol at steady state, measured by $AUC_{(0\text{-}24h)}$, 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 nonnucleoside 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.

Concomitant administration of strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. ketoconazole, itraconazole, fluconazole, voriconazole), cimetidine, verapamil, macrolides (e.g. erythromycin, clarithromycin and roxithromycin), diltiazem, protease inhibitors (e.g. ritonavir, saquinavir, indinavir, nelfinavir), antidepressants (e.g. nefazodone, fluvoxamine, fluoxetine), and grapefruit juice may increase plasma levels of progestogens (dienogest) and result in undesirable effects.

In a 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% (2.9-fold) increase of $AUC_{(0\text{-}24h)}$ at steady-state for dienogest. When co-administered with the moderate inhibitor erythromycin, the $AUC_{(0\text{-}24h)}$ of dienogest at steady state were increased by 62% (1.6-fold).

The clinical relevance of potential interactions with enzyme inhibitors remains unknown.

Effects of Dienogest on other Medicinal Products

Based on *in vitro* inhibition studies, a clinically relevant interaction of dienogest with the CYP450

enzyme-mediated metabolism of other medication is unlikely.

Interaction with Food

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

Use in Special Population

Patients with Renal Impairment

Dienogest has not been studied specifically in renally impaired subjects. However, no special risk for these patients is expected since dienogest is almost completely metabolized before excretion and the metabolites are pharmacologically inactive. There are no data suggesting the need for a dosage adjustment in patients with renal impairment.

Patients with Hepatic Impairment

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

Pregnant Women

The administration of dienogest during pregnancy is contraindicated. If pregnancy occurs during use of dienogest, use of the product must be discontinued.

There is limited data from the use of dienogest in pregnant women. To date, no significant epidemiological data has been obtained. Preclinical data reveal no special risks on pregnancy, embryonic/foetal development, birth or development after birth for humans. 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 foetus/newborn. However, dienogest must not be administered to pregnant women because there is no need to treat endometriosis during pregnancy.

Lactating Women

Treatment with dienogest during lactation is not recommended.

It is unknown whether dienogest is excreted in human milk. Physiochemical properties and data in animals have shown excretion of dienogest in rat milk. A decision must be made whether to discontinue breastfeeding or to abstain from dienogest therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Pediatric Patients

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

Geriatric Patients

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

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.

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 pattern, such as spotting, irregular bleeding or amenorrhoea. The most frequently reported undesirable effects under treatment with dienogest are headache (9%), breast discomfort (5.4%), depressed mood (5.1%) and acne (5.1%).

In addition, the majority of patients treated with dienogest experience changes in their menstrual bleeding pattern. Menstrual bleeding patterns were assessed systematically using patient diaries and were analysed using the WHO 90-days reference period method. During the first 90 days of treatment with dienogest, 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.

System Organ Class	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**
Blood and lymphatic system disorders		Anaemia
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 Onychoclasis 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 engorgement Breast pain 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	Asthenic conditions Irritability	Oedema

Decrease of BMD

In an uncontrolled clinical trial with 111 adolescent women (12 to <18 years of age) 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.

Reporting of side effects

If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024 or you can report to Cipla Ltd on 18002677779. By reporting side effects, you can help provide more information on the safety of this product.

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 (10-15 times higher dose than in dienogest) over 24 weeks of use was very well tolerated.

Pharmacological Properties

Mechanism of Action

Dienogest acts on endometriosis by reducing the endogenous production of oestradiol and, thereby, suppresses the trophic effects of oestradiol 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 and to the reduction of pelvic pain associated with endometriosis.

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

Pharmacodynamic Properties

Dienogest is a nortestosterone derivative with no androgenic but rather an antiandrogenic activity of approximately one-third of that of cyproterone acetate. It is a selective progestin, combining the pharmacological properties of 19-norprogestins with progesterone derivatives, and has a pronounced effect on endometrial tissue. 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*.

Efficacy

Superiority of dienogest over placebo with regard to reduction of endometriosis-associated pelvic pain (EAPP) and clinically meaningful reduction of pain compared to baseline were demonstrated in a 3-month study including 102 patients on dienogest. EAPP was measured on a Visual Analog Scale (VAS) (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 ± 22.9) were demonstrated.

After 3 months of treatment, reduction of EAPP 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 EAPP 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 showed a continued improvement of endometriosis-associated pelvic pain for a treatment duration of up to 15 months (mean reduction at end of treatment = 43.2 ± 21.7 mm).

In addition, efficacy on EAPP was shown in a 6-months comparative trial of dienogest versus the GnRH analogue leuprorelin acetate (LA) including 120 patients on dienogest. EAPP was measured on a VAS (0 – 100 mm). A clinically meaningful reduction of pain compared to baseline and statistical non-inferiority versus LA were demonstrated (dienogest 47.5 ± 28.8 mm, LA 46.0 ± 24.8 mm). Non-inferiority versus LA based on a pre-defined non-inferiority margin of 15 mm was demonstrated ($p < 0.0001$).

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.

A randomised, double-blind, parallel-group study (n = 20 to 23 per dose group) investigated

pharmacodynamic effects of four dienogest doses (0.5, 1.0, 2.0 or 3.0 mg/day) for a maximum of 72 days. Ovulations were observed in 14% and 4% of women of the 0.5 mg and 1 mg groups, respectively. No ovulations occurred in the 2 mg and 3 mg groups. Dienogest has not been tested for contraceptive efficacy in larger studies.

The efficacy of dienogest was demonstrated in the treatment of endometriosis related symptoms (pelvic pain, dysmenorrhea and dyspareunia) in a 12 month study with 111 female adolescents (after menarche between 12 and < 18 years of age).

Safety

Endogenous oestrogen levels are only moderately suppressed during treatment with dienogest.

Bone mineral density (BMD) was assessed in 21 adult patients before and after 6 months of treatment and there was no reduction in the mean BMD. In a 12 month study involving 103 adolescents the mean relative change in BMD of the lumbar spine (L2-L4) from baseline to the end of treatment (EOT) was -1.2% (95% CI: -1.70% and -0.78%). In a subset of patients with decreased BMD at the EOT (n = 60), a follow-up measurement performed 6 months after cessation of treatment showed an increase in BMD towards baseline levels (mean relative change from baseline: -2.3% at EOT and -0.6% at 6 months after EOT [95% CI: -1.20% and 0.06%]).

No significant impact on standard laboratory parameters, including haematology, blood chemistry, liver enzymes, lipids, and HbA1C was observed during treatment with dienogest for up to 15 months (n = 168).

Pharmacokinetic Properties

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 and linear 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). Upto 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.

Steady-State Conditions

Pharmacokinetics of dienogest are 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 can be predicted from single-dose pharmacokinetics. 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.

Metabolism

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.

Excretion

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 the 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.

Nonclinical Properties

Animal Toxicology

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.

Long-term studies in rats and mice with dienogest showed increased incidences of pituitary adenomas, fibroepithelial mammary tumours, stromal polyps of the uterus and malignant lymphoma, at doses corresponding to exposure levels about 10 times that anticipated at the maximum recommended clinical dose, based on area under the plasma concentration time curve (AUC). Similar tumours have been shown to develop with other oestrogenic/progestogenic compounds. The tumours are thought to result from marked species differences in the optimal oestrogen:progestogen ratio for reproductive function. Dienogest showed no tumour promotion activity in the rat liver foci assay at exposure levels corresponding to >100 times the estimated human exposure at the clinical dose, based on AUC.

Dienogest did not exhibit any evidence of genotoxic potential in assays for gene mutations in bacterial or mammalian cells, *in vitro* and *in vivo*.

Description

CIPGEST tablet contains 2 mg of dienogest, a selective progestin.

Pharmaceutical Particulars

Shelf-life

18 months

Packaging Information

CIPGEST is available in a pack of 10 tablets.

Storage and Handling Instructions

Store in the original packaging to protect from light.

Keep out of the reach and sight of children. Do not use **CIPGEST** after the expiry date.

Patient Counselling Information

1. **What is CIPGEST and what is it used for?**

CIPGEST is a preparation for the management of pelvic pain associated with endometriosis (painful symptoms due to displaced tissue of the lining of the womb). **CIPGEST** contains a hormone, the progestogen dienogest.

1. **What you need to know before you take CIPGEST?**

DO NOT take dienogest if you:

- are suffering from a blood clot (thromboembolic disorder) in your veins. 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 severe arterial disease, 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 tumour
- suffer or have ever suffered, or if it is suspected that you suffer from a malignant sex-hormone dependent tumour such as cancer of the breast or the genital organs
- have any unexplained vaginal bleeding
- are allergic (hypersensitive) to dienogest or any of the other ingredients of this medicine

If any of these conditions appear for the first time while using dienogest, stop taking it at once and consult your doctor.

Warnings and Precautions

You must not use hormonal contraceptives of any form (tablet, patch, intrauterine system) while taking dienogest.

Dienogest is NOT a contraceptive. If you want to prevent pregnancy, you should use condoms or other nonhormonal contraceptive precautions.

In some situations, you need to take special care while using dienogest, and your doctor may need to examine you regularly. Tell your doctor if any of the following conditions applies to you. If you:

- have ever had a **blood clot** (venous thromboembolism) or anyone in your immediate family has had a blood clot at a relatively early age
- have a close relative who has had **breast cancer**
- have ever suffered from **depression**
- have **high blood pressure** or develop high blood pressure while taking dienogest
- develop a **liver disease** while taking dienogest. 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 previous pregnancy
- have ever had **chloasma** (golden-brown patches on the skin, particularly of the face); if so, avoid too much exposure to the sun or ultraviolet radiation
- suffer from **pain in your lower abdomen** while taking dienogest

While taking dienogest your chance of becoming pregnant is reduced because dienogest may affect ovulation.

If you become pregnant while taking dienogest you are at **a slightly increased risk** of having an extrauterine pregnancy (the embryo develops outside the womb). Tell your doctor before you start taking dienogest, if you had an extrauterine pregnancy in the past or have an impaired function of the Fallopian tubes.

Dienogest and Serious Uterine Bleeding

Uterine bleeding, for example in women with a condition where the mucous membrane of your uterus (endometrium) grows into the muscle layer of your uterus, called adenomyosis uteri or **benign tumours of the womb** sometimes called uterine fibroids (uterine leiomyomata), may become worse with the use of dienogest. If bleeding is heavy and continuous over time, this may lead to low red blood cell levels (anaemia), which may be severe in some cases. In the event of anaemia, you should discuss with your doctor if you should stop taking dienogest.

Dienogest and Changes in Bleeding Pattern

Most women treated with dienogest experience changes in their menstrual bleeding pattern.

Dienogest and Venous Blood Clots

Some studies indicate that there may be a slight, but not statistically significant, increased risk of a **blood clot in the legs (venous thromboembolism)** associated with the use of preparations with progestagens like dienogest. Very rarely, blood clots may cause serious permanent disabilities or may even be fatal. The risk of a **venous blood clot** increases:

- with increasing age
- if you are overweight
- if you or one of your close relatives had a blood clot in the leg (thrombosis), lung (pulmonary embolism), or other organ at a young age.
- if you must have surgery, if you have had a serious accident or if you are immobilized for a long time. It is important to tell your doctor in advance that you are using dienogest as the treatment may have to be stopped. Your doctor will tell you when to start dienogest again. This is usually about two weeks after you are back on your feet.

Dienogest and Arterial Blood Clots

There is little evidence for an association between preparations with progestagens like dienogest and an increased risk of a blood clot in, for example, the blood vessels of the heart (heart attack) or the brain (stroke). In women with hypertension the risk of stroke may be slightly enhanced by these preparations. The risk of an **arterial blood clot** increases:

- **if you smoke. You are strongly advised to stop smoking when you use dienogest, especially if you are older than 35 years.**

- if you are overweight
- if one of your close relatives had a heart attack or stroke at a young age
- if you have high blood pressure

Talk to your doctor before taking dienogest.

Stop taking dienogest and contact your doctor immediately if you notice possible signs of a blood clot, such as:

- severe pain and/or swelling in one of your legs

- sudden severe pain in the chest which may reach the left arm

- sudden breathlessness

- sudden cough without an obvious cause

- any unusual, severe or long-lasting headache or worsening of migraine

- partial or complete blindness or double vision

- difficulty in speaking or inability to speak

- giddiness or fainting

- weakness, strange feeling, or numbness in any part of the body

Dienogest and Cancer

It is not clear from the data currently available whether or not dienogest increases the risk of breast cancer. Breast cancer has been observed slightly more often in women taking hormones compared to those not taking hormones, but it is not known whether this is caused by the treatment. For example, it may be that more tumours are detected and detected earlier in women taking hormones because they are examined by their doctor more often. The occurrence of breast tumours becomes gradually less after stopping the hormone treatment. **It is important to regularly check your breasts** and you should contact your doctor if you feel any lump.

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

Dienogest and Osteoporosis

Changes in Bone Mineral Density (BMD)

The use of dienogest may affect the strength of the bone of adolescents (12 to under 18 years). If you are under 18 your doctor will, therefore, carefully weigh the benefits and risks of using dienogest for you as an individual patient, taking into account possible risk factors for bone loss (osteoporosis).

If you use dienogest, it will help your bones if you have an adequate intake of calcium and vitamin D either via your food or via supplements.

If you have an increased risk of getting osteoporosis (weakening of bones due to loss of bone

minerals), your doctor will carefully weigh the risks and benefits of treatment with dienogest because dienogest has a moderate suppressing effect on the production of oestrogen (another type of female hormone) by your body.

Other Medicines and Dienogest

Always tell your doctor which medicines or herbal products you are already using. Also tell any other doctor or dentist who prescribes another medicine (or the pharmacist) that you are taking dienogest.

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

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

Ask your doctor or pharmacist for advice before taking any medicine.

Dienogest with Food and Drink

During dienogest treatment, you should avoid drinking grapefruit juice, because this may increase the levels of dienogest in your blood. This may increase the risk of getting side effects.

Laboratory Tests

If you need a blood test, tell your doctor or the laboratory staff that you are taking dienogest, because dienogest can affect the results of some tests.

Pregnancy, Breastfeeding and Fertility

Do not take dienogest if you are pregnant or breastfeeding.

Driving and using Machines

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

Children and Adolescents

Dienogest is not for use in girls before menarche (first menstrual bleeding).

The use of dienogest may affect the strength of the bone of adolescents (12 to under 18 years). If you are under 18 your doctor will, therefore, carefully weigh the benefits and risks of using dienogest for you as an individual patient, taking into account possible risk factors for bone loss (osteoporosis).

1. **How to take CIPGEST**

Always take **CIPGEST** exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. For adults, the usual dose is 1 tablet per day.

The following statements apply to **CIPGEST** unless otherwise prescribed by your doctor. Please follow these instructions, otherwise you will not fully benefit from dienogest. You can start treatment with dienogest on any day of your natural cycle.

Adults: take one tablet every day, preferably at the same time with some liquid as needed. When a pack is finished the next one should be started without interruption. Continue to take the tablets also on days of menstrual bleeding.

There is no experience with dienogest treatment > 15 months in patients with endometriosis.

If you take more CIPGEST than you should

There have been no reports of serious harmful effects from taking too many **CIPGEST** tablets at one time. However, if you are concerned, contact your doctor.

If you forget to take CIPGEST or suffer from vomiting or diarrhoea

CIPGEST will be less effective if you miss a tablet. If you miss one or more tablets, take one tablet only as soon as you remember, and then continue next day taking the tablet at your usual time.

If you vomit within 3-4 hours of taking **CIPGEST** or you have severe diarrhoea, there is a risk that the active substance in the tablet will not be taken up by your body. The situation is almost the same as forgetting a tablet. After vomiting or diarrhoea within 3-4 hours of taking **CIPGEST**, you should take another tablet as soon as possible.

Do not take a double dose to make up for a forgotten tablet.

If you stop taking CIPGEST

If you stop taking **CIPGEST**, your original endometriosis symptoms may return.

1. **Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them. These effects are more common during the first months after start of intake of dienogest and usually disappear with continued use. You may also experience changes in your bleeding pattern, such as spotting, irregular bleeding or your periods may stop completely.

Common (affecting between 1 and 10 in every 100 users)

- weight gain
- depressed mood, problems sleeping, nervousness, loss of interest in sex, or changed mood
- headache or migraine
- nausea, abdominal pain, wind, swollen tummy or vomiting
- acne or hair loss
- back pain
- breast discomfort, ovarian cyst or hot flushes
- uterine/vaginal bleeding including spotting
- weakness or irritability

Uncommon (affecting between 1 and 10 in every 1,000 users)

- anaemia
- weight loss or increase in appetite
- anxiety, depression or mood swings
- imbalance in the autonomic nervous system (controls unconscious bodily functions, e.g. perspiration) or disturbed attention
- dry eye
- tinnitus
- unspecific circulatory problems or uncommon palpitations
- low blood pressure
- shortness of breath
- diarrhoea, constipation, abdominal discomfort, inflammation of the stomach and intestines (gastrointestinal inflammation), inflammation of the gums (gingivitis)
- dry skin, excessive sweating, severe itching of the whole body, male pattern hair growth (hirsutism),
- brittle nails, dandruff, dermatitis, abnormal hair growth, hypersensitive response to light or problems with skin pigmentation
- pains in your bones, muscle spasms, pains and/or a sensation of heaviness in your arms and hands or legs and feet
- urinary tract infection
- vaginal thrush, dryness of the genital area, vaginal discharge, pelvic pain, atrophic inflammation of the genitals with discharge (atrophic vulvovaginitis), or a lump or lumps in the breast
- swelling due to fluid retention

Additional side effects in adolescents (12 to under 18 years): loss of bone density.

Reporting of side effects

If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024 or you can report to Cipla Ltd on 18002677779. By reporting side effects, you can help provide more information on the safety of this product.

1. **How to store CIPGEST**

Store in the original packaging to protect from light.

Keep out of the reach and sight of children. Do not use **CIPGEST** after the expiry date.

1. **Contents of the pack and other information**

CIPGEST is available in a pack of 10 tablets.

Details of Manufacturer

Plot No. 56-57, Sector 6A IIE (SIDCUL), Ranipur (BHEL), Haridwar - 249403 (INDIA)

Details of Permission or Licence Number with Date

27/UA/SC/P- 2018 – 22- Nov – 2018

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