Professional Information

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

DIENTERNA, 2 mg, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg dienogest.

Excipient(s) with known effect:

- Contains sugar (lactose monohydrate): 62,8 mg per tablet.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DIENTERNA is indicated for the treatment of endometriosis.

Safety and efficacy beyond 24 months have not been established.

4.2 Posology and method of administration

Posology

Tablet-taking from the very first pack should start on day 1 of the woman’s natural cycle (i.e. the first day of her menstrual bleeding). The dosage of DIENTERNA is one tablet

daily without any break, taken preferably at the same time each day with some liquid as needed.

Tablets must be taken throughout 28 days without regard for bleeding. When a pack is finished the next one should be started without interruption.

The efficacy of DIENTERNA may be reduced in the event of missed tablets, vomiting, and/ or diarrhoea (if occurring within 3 to 4 hours after tablet taking). In the event of missed tablet(s), the woman should take one tablet only, as soon as she remembers, and should then continue next day to take tablet at her usual time. A tablet not absorbed due to vomiting or diarrhoea should likewise be replaced by one tablet.

Method of administration

For oral use.

4.3 Contraindications

DIENTERNA should not be used in the presence of any condition listed below. Should any of the conditions appear during the use of DIENTERNA, the use of DIENTERNA must be discontinued immediately:

- Hypersensitivity to dienogest or to any of the excipients listed in section 6.1.
- Known or suspected pregnancy (see section 4.6).
- Breastfeeding (see section 4.6).
- History of or active venous thromboembolic disorder.
- Arterial and cardiovascular diseases, past or present (e.g. myocardial infarction, cerebrovascular events, 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.

4.4 Special warnings and precautions for use

Serious uterine bleeding

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

Changes in menstrual bleeding pattern

The majority of patients treated with DIENTERNA experience changes in their menstrual bleeding pattern (see section 4.8).

Circulatory disorders

From epidemiological studies there is little evidence for an association between progestogen-only preparations as in DIENTERNA 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 DIENTERNA.
Although not statistically significant, some studies indicate that there may be a slightly increased risk of venous thromboembolism (deep venous thrombosis, pulmonary embolism) associated with the use of progestogen-only preparations. Generally recognized risk factors for venous thromboembolism (VTE) include a positive personal or family history (VTE in a sibling or a parent at a relatively early age), age, obesity, prolonged immobilization, major surgery or major trauma. In case of long-term immobilization, it is advisable to discontinue the use of DIENTERNA (in the case of elective surgery at least four weeks in advance) and not to resume treatment until two weeks after complete remobilization.

The increased risk of thromboembolism in the puerperium must be considered.
Treatment should be stopped at once if there are symptoms of an arterial or venous thrombotic event or suspicion thereof.

Tumours

There is a risk of having breast cancer diagnosed in patients using DIENTERNA.
In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of hormonal substances such as the one contained in DIENTERNA. 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 DIENTERNA.

Osteoporosis

Changes in bone mineral density (BMD).
The use of dienogest 2 mg (as in DIENTERNA) was monitored in adolescents (12 to <18 years) over a treatment period of 12 months. The use of dienogest 2 mg was associated with a decrease in bone mineral density (BMD) in the lumbar spine (L2-L4).

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

In patients who are at an increased risk of osteoporosis a careful risk-benefit assessment should be performed before starting DIENTERNA because endogenous estrogen levels are moderately decreased during treatment with DIENTERNA.

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

Other conditions

- Patients who have a history of depression should be carefully observed and the medicine discontinued if the depression recurs to a serious degree.
- Dienogest generally does not appear to affect blood pressure in normotensive women. However, if a sustained clinically significant hypertension develops during the use of DIENTERNA, it is advisable to withdraw therapy and treat the hypertension.
- Recurrence of cholestatic jaundice and/or pruritus which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of DIENTERNA.
- 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 DIENTERNA.
- 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 DIENTERNA.
- 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 DIENTERNA should be decided on only after carefully weighing the benefits against the risks.
- Patients are advised to use non-hormonal methods of contraception (barrier contraception, e.g. condom) to prevent unwanted pregnancies.
- Persistent ovarian follicles (often referred to as functional ovarian cysts) may occur during the use of DIENTERNA. Most of these follicles are asymptomatic,

although some may be accompanied by pelvic pain.

Lactose

DIENTERNA contains lactose (as lactose monohydrate):

- Patients with the rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take DIENTERNA.

4.5 Interactions with other medicines and other forms of interaction

Effects of other medicines on DIENTERNA

Individual enzyme-inducers or inhibitors (CYP3A4):

- Progestogens, including DIENTERNA, are metabolised mainly by the cytochrome P450 system (CYP3A4) located both in the intestinal mucosa and in the liver. Therefore, inducers or inhibitors of CYP3A4 may affect the metabolism of DIENTERNA.
- An increased clearance of sex hormones due to enzyme induction may reduce the therapeutic effect of DIENTERNA and may result in undesirable effects e.g. change in bleeding profile.
- A reduced clearance of sex hormones due to enzyme inhibition may increase the therapeutic effects of DIENTERNA and may result in undesirable effects.

Substances with enzyme-inducing properties:

- Interaction can occur with medicines (e.g. phenytoin, barbiturates, primidone, carbamazepine, rifampicin and possibly oxcarbazepine, topiramate, felbamate, griseofulvin, nevirapine and products containing St. John’s wort) that induces microsomal enzymes (e.g. cytochrome P450 enzymes) which can result in increased clearance of sex hormones and diminished efficacy of dienogest.
- Maximum enzyme induction is generally not seen for 2 to 3 weeks but may then be sustained for at least 4 weeks after cessation of therapy.

Substances with enzyme-inhibiting properties:

- Known CYP3A4 inhibitors like azole antifungals (e.g. ketoconazole, itraconazole, fluconazole), cimetidine, verapamil, macrolides (e.g. erythromycin, clarithromycin and roxithromycin), diltiazem, protease inhibitors (e.g. ritonavir, saquinavir, indinavir, nelfinavir), antidepressants (e.g. nefazodone, fluvoxamine, fluoxetine) may increase plasma levels of progestogens and result in undesirable effects.

Effects of DIENTERNA on other medicines

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

Other forms of interactions

The use DIENTERNA may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins (e.g.
corticosteroid binding globulin and lipid/lipoprotein fractions), parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

Interaction with food.

A standardized high fat meal did not affect the bioavailability of 2 mg dienogest tablets.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

The administration of DIENTERNA during pregnancy is contraindicated (see section 4.3).

If pregnancy occurs during the use of DIENTERNA, further intake should be stopped.

Breastfeeding

DIENTERNA should not be used by breastfeeding women (see section 4.3).

Fertility

Based on the available data, ovulation is inhibited in the majority of patients during treatment with DIENTERNA. However, DIENTERNA is not a contraceptive. If contraception is required a non-hormonal method should be used (see section 4.4).
Based on available data, the menstrual cycle returns to normal within 2 months after cessation of treatment with DIENTERNA.

4.7 Effects on ability to drive and use machines

DIENTERNA has no influence on the ability to drive and use machines.
No effects on the ability to drive or use machines have been observed in users of medicines containing dienogest.

4.8 Undesirable effects

a. Summary of the safety profile

Undesirable effects are more common during the first months after the start of treatment with DIENTERNA and subside with continued treatment.
There may be changes in bleeding pattern, such as spotting, irregular bleeding or amenorrhea. The following undesirable effects have been reported in users of dienogest (as in DIENTERNA). The most frequently reported undesirable effects are headache, breast discomfort, depressed mood and acne. Furthermore, the majority of patients treated experience changes in their menstrual bleeding pattern.
Changes in menstrual bleeding patterns were only occasionally reported as adverse event by the patients (See adverse event table).

b. Tabulated summary of adverse reactions

System Organ Class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Less frequent	Anaemia.
Metabolism and nutrition disorders	Frequent	Weight increased.
	Less frequent	Weight decreased, increased appetite.
Psychiatric disorders	Frequent	Depressed mood, sleep disorder, nervousness, loss of libido, altered mood.
	Less frequent	Anxiety, depression, mood swings.
Nervous system disorders	Frequent	Headache, migraine.
	Less frequent	Autonomic nervous system Imbalance, disturbance in attention.
Eye disorders	Less frequent	Dry eyes.
Ear and labyrinth disorders	Less frequent	Tinnitus.
Cardiac disorders	Less frequent	Unspecified circulatory system disorder, palpitations.
Vascular disorders	Less frequent	Hypotension.
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea.
Gastrointestinal disorders	Frequent	Nausea, abdominal pain, flatulence, abdominal distention, vomiting.

	Less frequent	Diarrhoea, constipation, abdominal discomfort, gastrointestinal inflammation, gingivitis.
Skin and subcutaneous tissue disorders	Frequent	Acne, alopecia.
	Less frequent	Dry skin, hyperhidrosis, pruritus, hirsutism, onychoclasis, dandruff, dermatitis, abnormal hair growth, photosensitivity reaction, pigmentation disorder.
Musculoskeletal and connective tissue disorders	Frequent	Back pain.
	Less frequent	Bone pain, muscle spasm, pain in extremity, heaviness in extremities.
Renal and urinary disorders	Less frequent	Urinary tract infection.
Reproductive system and breast disorders	Frequent	Breast discomfort, ovarian cyst, hot flush, uterine/vaginal bleeding including spotting.
	Less frequent	Vaginal candidiasis, vulvovaginal dryness, genital discharge, pelvic pain, atrophic vulvovaginitis, breast mass, fibrocystic breast diseases, breast induration.
General disorders and administrative site conditions	Frequent	Asthenic conditions, irritability.
	Less frequent	Oedema.

c. Description of selected adverse reactions

Uterine bleeding irregularities:

The following bleeding patterns were observed: amenorrhea, infrequent bleeding, frequent bleeding, irregular bleeding, prolonged bleeding, and normal bleeding.

Decrease of bone mineral density:

In an uncontrolled study with 111 adolescent women (12 to <18 years) who were treated with dienogest 2 mg, 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 (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

Acute toxicity studies performed with dienogest (as in DIENTERNA) did not indicate a risk of acute adverse effects in case of inadvertent intake of a multiple of the daily therapeutic dose. A daily intake of 20 to 30 mg dienogest (10 to 15 times higher dose than in DIENTERNA) over 24 weeks of use was very well tolerated. However, overdosage may potentiate the adverse

effects reported under section 4.4 ("Special warnings and precautions for use") and section 4.8 ("Undesirable effects").

Treatment

There is no specific antidote, treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.8.2 Progesterones with or without estrogens.

Pharmacotherapeutic group: Progestogens. ATC Code: G03D.

Mechanism of action

Dienogest is a nortestosterone derivative with no androgenic but rather antiandrogenic activity of approximately one third of that of cyproterone acetate. Dienogest binds to the progesterone receptor of the human uterus with only 10 % of the relative affinity of progesterone. Despite its low affinity to the progesterone receptor, dienogest has a strong progestogenic effect *in vivo*. Dienogest has no significant androgenic, mineralocorticoid or glucocorticoid activity *in vivo*.

Dienogest acts on endometriosis by reducing the endogenous production of oestradiol and thereby suppresses the trophic effects of estradiol on both the eutopic and ectopic endometrium. When given continuously, dienogest leads to a hypoestrogenic, hypergestagenic endocrine environment causing initial decidualization of endometrial tissue followed by atrophy of endometriotic lesions.

5.2 Pharmacokinetic properties

Absorption

Orally administered dienogest is almost completely absorbed. Peak serum concentrations of 47 ng/mL are reached at about 1,5 hours after ingestion of dienogest. Bioavailability is about 91 %.

The pharmacokinetics of dienogest are dose-proportional within the dose range of 1 to 8 mg.

A standardised high fat meal does not affect the bioavailability of dienogest.

Distribution

Dienogest is bound to serum albumin and does not bind to sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG). 10 % of the total serum concentration of the active substance is present as free steroid, 90 % is non-specifically bound to albumin. The apparent volume of distribution (V_d/F) of dienogest is 40 litres.

Biotransformation

Dienogest is completely metabolised by the known pathway of steroid metabolism, with the formation of endocrinologically mostly inactive metabolites. Based on the *in vivo* and *in vitro* studies, CYP3A4 is the major enzyme involved in the metabolism of dienogest. The metabolites are rapidly excreted so that in plasma, unchanged dienogest is the dominating fraction. The metabolic clearance rate from serum Cl/F is 64 mL/min.

Elimination

Dienogest serum levels decrease in two phases. The terminal disposition phase is characterised by a half-life of approximately 9 to 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 is excreted within the first 24 hours, mostly with the urine.

Steady-state condition

The pharmacokinetics of dienogest after repeated administration of DIENTERNA can be predicted from single dose pharmacokinetics.

Pharmacokinetics in special population

Dienogest has not been studied specifically in renally impaired subjects.

Dienogest has not been studied in subjects with hepatic impairment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone

Lactose monohydrate

Magnesium Stearate

Microcrystalline Cellulose

Potato starch

Povidone

Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C

Store in the original packaging to protect from light.

6.5 Nature and contents of container

The tablets are contained in green PVC-PVDC blister packs with aluminium foil lidding in a cardboard carton.

They are supplied in a blister pack containing 14 tablets.

Boxes contain 28, 84 or 168 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

TRINITY PHARMA (PTY) LTD

106 16th Road,

Midrand,

1686

South Africa

8. REGISTRATION NUMBER(S)

55/21.8.2/0896

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORIZATION

01 August 2023

10. DATE OF REVISION OF THE TEXT

N/A