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SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

DIENOGEST 2 mg DYNA tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg dienogest.

Each tablet contains sugar (lactose monohydrate 60,93 mg).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet.

DIENOGEST 2 mg DYNA tablets are white, round, biconvex and plain, with a diameter of 5 mm approximately and thickness about 3 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of endometriosis.

DIENOGEST 2 mg DYNA is indicated in the long-term treatment of endometriosis in adolescents after menarche from 12 years of age onward and adults

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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 DIENOGEST 2 mg DYNA 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.

Management of missed tablets

The efficacy of DIENOGEST 2 mg DYNA 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.

Patients should not take a double dose to compensate for the missed dose.

Special populations

Elderly

There is no relevant indication for use of DIENOGEST 2 mg DYNA in the elderly population.

Patients with hepatic impairment

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DIENOGEST 2 mg DYNA is contraindicated in patients with present or past severe hepatic disease. (see section 4.3).

Patients with renal impairment

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

Paediatric population

DIENOGEST 2 mg DYNA is not indicated in children prior to menarche. The efficacy of DIENOGEST 2 mg DYNA has been demonstrated in the treatment of endometriosis – associated pelvic pain in adolescent patients (12-18 years), with an overall favourable safety and tolerability profile.

The use of DIENOGEST 2 mg DYNA in adolescents over a treatment period of 12 months was associated with a mean decrease in Bone Mineral Density (BMD) in the lumbar spine of 12 %. After cessation of treatment, BMD increased again in these patients.

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 medical practitioner should weigh the benefits of DIENOGEST 2 mg DYNA against the possible risks of use in each individual adolescent patient (see “section 4.4” and “section 5.1’).

Method of administration

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For oral use.

One DIENOGEST 2 mg DYNA tablet is to be swallowed daily, without any break, with some liquid as needed.

4.3 Contraindications

DIENOGEST 2 mg DYNA should not be used in the presence of any of the conditions listed below. Should any of the conditions appear during therapy, the use of DIENOGEST 2 mg DYNA must be discontinued immediately:

- hypersensitivity to dienogest or to any of the excipients of DIENOGEST 2 mg DYNA (see section 6.1)

- 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) or active liver disease
- known or suspected sex hormone-dependent malignancies
- undiagnosed vaginal bleeding.
- personal and family history of breast cancer
- previous proven deep-vein thrombosis (DVT) or current active venous thromboembolic disorder

- previous pulmonary embolism
- inherited thrombophilia
- patients known with inherited genetic mutations: BRCA1 and BRCA 2 genes
- early menstrual periods (before the age of 12 years)
- history of non-cancerous breast diseases (atypical hyperplasia or lobular carcinoma in situ)
- previous treatment using radiation therapy to the chest or breast
- previous exposure to diethylstilbestrol (DES)

4.4 Special warnings and precautions for use

As DIENOGEST 2 mg DYNA 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 2 mg DYNA although not all of the warnings and precautions are based on respective findings in clinical studies with dienogest 2 mg as in DIENOGEST 2 mg DYNA.

If any of the conditions/risk factors mentioned below is present or deteriorates, an individual risk-benefit analysis should be done before treatment with DIENOGEST 2 mg DYNA can be started or continued.

Serious uterine bleeding

Uterine bleeding, for example in women with adenomyosis uteri or uterine leiomyomata, may be aggravated with the use of DIENOGEST 2 mg DYNA. 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 2 mg DYNA should be considered.

Changes in bleeding pattern

The majority of patients treated with DIENOGEST 2 mg DYNA 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, such as DIENOGEST 2 mg DYNA 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, such as DIENOGEST 2 mg DYNA.

Some epidemiological studies indicate a trend, but not statistically significant increased risk of venous thromboembolism (deep venous thrombosis, pulmonary embolism) associated with the use of progestogen only medicines such as DIENOGEST 2 mg DYNA. Generally recognised risk factors for venous thromboembolism (VTE) include a positive personal or family history (VTE in a sibling or a parent at a relatively young age), age, obesity, prolonged immobilisation, major surgery or major trauma. In case of long-term immobilisation, it is advisable to discontinue the use of DIENOGEST 2 mg DYNA (in the case of elective surgery

at least four weeks in advance)and not to resume treatment until two weeks after complete remobilisation.

The increased risk of thromboembolism in the puerperium must be considered.

Treatment should be stopped at once if there are symptoms of an arterial or venous thrombotic event or suspicion thereof.

Breast cancer

DIENOGEST 2 mg DYNA contains dienogest, which on prolonged use, may increase the risk of developing breast cancer. A meta-analysis of prospective epidemiological studies from 1992 to 2018 reported a significant increase in the risk of developing breast cancer in 55,575 women 40 - 59 years of age who used menopausal hormone therapy (MHT). The risk increased steadily with duration of use and was slightly greater for oestrogen-progestogen than oestrogen only preparations, and the risk persisted for more than 10 years after stopping the treatment. The relative risk (RR) to develop breast cancer for oestrogen-progestogen preparations was 1.60 at 1-4 years and RR=2.08 at 5-14 years, while that for oestrogen only preparations was 1.17 at 1-4 years and 1.33 at 5-14 years.
There was no risk of to develop breast cancer in women who started MHT at 60 years of age.

All women on DIENOGEST 2 mg DYNA should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. Mammography evaluations should be done based on patient age, risk factors, and prior mammogram results.

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Tumours

There is an increased risk of having breast cancer diagnosed in patients taking DIENOGEST 2 mg DYNA.

Cases of benign liver tumours and, even more rarely, malignant liver tumours have been reported in users of hormonal medicines such as DIENOGEST 2 mg DYNA. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages.

Changes in bone mineral density (BMD)

The use of DIENOGEST 2 mg DYNA in adolescents (12 to 18 years) over a treatment period of 12 months was associated with a mean decrease in bone mineral density (BMD) in the lumbar spine of 1.2%. After cessation of treatment, BMD increased again in these patients. 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 (see sections 4.2 and section 5.1).

Therefore, the treating doctor should weigh the benefits of DIENOGEST 2 mg DYNA 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 drugs that can reduce bone mass, e.g. anticonvulsants or corticosteroids, previous low trauma fracture, alcohol abuse and/or smoking).

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

No BMD decrease was observed in adults (see section 5.1).

Other conditions

Patients who have a history of depression should be carefully observed and DIENOGEST 2 mg DYNA discontinued if the depression recurs to a serious degree.

DIENOGEST 2 mg DYNA generally does not appear to affect blood pressure in normotensive women. However, if a sustained clinically significant hypertension develops during DIENOGEST 2 mg DYNA therapy, it is advisable to withdraw DIENOGEST 2 mg DYNA and treat the hypertension.

DIENOGEST 2 mg DYNA should be discontinued in the event of recurrence of cholestatic jaundice and/ or pruritus which occurred first during pregnancy or previous use of sex steroids.

DIENOGEST 2 mg DYNA may have an effect on peripheral insulin resistance and glucose tolerance. Diabetic women, especially those with a history of gestational diabetes mellitus, should be carefully observed for uncontrolled glucose levels while taking DIENOGEST 2 mg DYNA.

Pregnancies that occur among users of progestogen-only medicines are more likely to be ectopic than are pregnancies among users of combined oral contraceptives.

Therefore, therapy with DIENOGEST 2 mg DYNA should be carefully considered, weighing the benefits against the risks, in women with a history of extra-uterine pregnancy or an impairment of tube function.

Patients are advised to use non-hormonal methods of contraception (barrier contraception, e.g. condom) to prevent unwanted pregnancies.

Chloasma may occasionally occur, especially in women with history of chloasma gravidarum. Exposure to the sun or ultraviolet radiation whilst taking DIENOGEST 2 mg DYNA should be avoided by women with a tendency to chloasma.

Persistent ovarian follicle (often referred to as functional ovarian cyst) may occur during DIENOGEST 2 mg DYNA therapy. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain.

Excipients

DIENOGEST 2 mg DYNA contains lactose monohydrate. Patients with the rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take DIENOGEST 2 mg DYNA.

4.5 Interaction with other medicines and other forms of interaction

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

Effects of other medicines on DIENOGEST 2 mg DYNA

Individual enzyme-inducers or inhibitors (CYP3A4)

Progestogens, including DIENOGEST 2 mg DYNA, 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 progesterone metabolism of DIENOGEST 2 mg DYNA.

An increased clearance of sex hormones due to enzyme induction may reduce the therapeutic effect of DIENOGEST 2 mg DYNA and may result in undesirable effects.

A reduced clearance of sex hormones due to enzyme inhibition may increase the therapeutic effects of DIENOGEST 2 mg DYNA 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 oxcarbazepine, topiramate, felbamate, griseofulvin, and products containing St. John's wort *(Hypericum perforatum)*.

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

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The effect of the CYP3A4 inducer rifampicin was studied in healthy postmenopausal women. Coadministration of rifampicin with estradiol valerate/dienogest tablets led to significant decreases in steady state concentrations and systemic exposures of dienogest and estradiol. The systemic exposure of dienogest and estradiol at steady state, measured by area under the curve (AUC) (0-24h), were decreased by 83 % and 44 %, respectively.

Substances with variable effects on the clearance of sex hormones, e.g.:
When co-administered with sex hormones, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of the progestin. These changes may be clinically relevant in some cases.

Substances decreasing the clearance of progestins (enzyme inhibitors) Dienogest is a substrate of cytochrome
Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, fluconazole, voriconazole, ketoconazole), verapamil, macrolides (e.g. erythromycin, clarithromycin), diltiazem, and grapefruit juice can increase plasma concentrations of the progestin.

Effects of DIENOGEST 2 mg DYNA on other medicines

Based on *in vitro* inhibition studies, a clinically relevant interaction of DIENOGEST 2 mg DYNA with the cytochrome P450 enzyme mediated metabolism of other medicines is unlikely.

Other forms of interaction

Laboratory tests

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of dienogest in pregnant women. Animal studies and data from women exposed to dienogest during pregnancy reveal no special risks on pregnancy, embryonic/ foetal development, birth or development after birth for humans. However, DIENOGEST 2 mg DYNA should not be administered to pregnant women because there is no need to treat endometriosis during pregnancy.

Breastfeeding

Treatment with DIENOGEST 2 mg DYNA during lactation is not recommended.

Physiochemical properties and animal data indicate excretion of dienogest in breast milk.

Fertility

Based on the available data, ovulation is inhibited in the majority of patients during treatment with DIENOGEST 2 mg DYNA.

However, DIENOGEST 2 mg DYNA is not a contraceptive.

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If contraception is required, a non-hormonal method should be used (See section 4.2).

Based on available data, the menstrual cycle returns to normal within 2 months after cessation of treatment with DIENOGEST 2 mg DYNA.

4.7 Effects on ability to drive and use machines

DIENOGEST 2 mg DYNA is not expected to affect the ability to drive and use machines.

4.8 Undesirable effects

a). Summary of the safety profile

Undesirable effects are more frequent during the first months after the start of treatment with DIENOGEST 2 mg DYNA. In addition to effects listed under section 4.4, the following undesirable effects have been reported in users of dienogest..

b). Tabulated summary of adverse reactions

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Less frequent	Anaemia

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Metabolism and nutrition disorders	Frequent Less frequent	Weight increased Weight decreased, increased appetite
Psychiatric disorders	Frequent Less frequent	Depressed mood, sleep disorder, nervousness, loss of libido, mood altered Anxiety, depression, mood swings
Nervous system disorders	Frequent Less frequent	Headache, migraine Autonomic nervous system imbalance, disturbance in attention
Eye disorders	Less frequent	Dry eyes
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Less frequent	Unspecific circulatory system disorder (deep vein thrombosis, pulmonary embolism), palpitations

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Vascular disorders	Less frequent	Hypotension
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea
Gastrointestinal disorders	Frequent	Nausea, abdominal pain, flatulence, abdominal distension, vomiting
	Less frequent	Diarrhoea, constipation, abdominal discomfort, gastrointestinal inflammation, gingivitis

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Skin and subcutaneous tissue disorders	Frequent Less frequent	Acne, alopecia Dry skin, hyperhidrosis, pruritus, hirsutism, onychoclasis, dandruff, dermatitis, abnormal hair growth, photosensitivity reaction, pigmentation disorders
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent	Back pain 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 flushes, uterine/vaginal bleeding including spotting
	Less frequent	Vaginal candidiasis, vulvovaginal dryness, genital discharge, pelvic pain, atrophic vulvovaginitis, breast mass, fibrocystic breast disease, 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 clinical trial with 111 adolescent women (12 to <18 years) who were treated with dienogest, as in DIENOGEST 2 mg DYNA, 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 requested to report any suspected adverse reactions to SAHPRA via Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 OVERDOSE

Signs and symptoms

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. 20 to 30 mg dienogest per day (10 to 15 times higher dose than in DIENOGEST 2 mg DYNA) over 24 weeks of use were very well tolerated. However, overdosage may potentiate the adverse effects reported under Side Effects (section 4.8).

Management of overdose

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

5. PHARMACOLOGICAL PROPERTIES

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5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens

ATC code: G03DB08

Pharmacological classification: A 21.8.2 Progesterones with or without estrogens

Mechanism of action

Dienogest is a nortestosterone derivative with no androgenic activity. Dienogest binds to the progesterone receptor of the human uterus with only 10 % of the relative affinity of progesterones. 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 abolishing the trophic effects of estradiol on both the eutopic and ectopic endometrium. When given continuously, dienogest leads to a hypoestrogenic, hypergestagenic endocrine environment and decidualisation of endometrial tissue.

5.2 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. A standardised high fat meal did not affect the bioavailability of dienogest. Bioavailability is about 91 %.

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The pharmacokinetics of dienogest is 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).

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 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 dienogest can be predicted from single dose pharmacokinetics.

Pharmacokinetics in special patient groups

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

Lactose monohydrate

Maize starch

Povidone K-30

Vegetable magnesium stearate

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 package in order to protect from light.

6.5 Nature and contents of container

Aluminium-PVC/PVDC blister strips.

Pack size of 28 tablets in a blister, such that one blister is packed into a printed outer carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

56/21.8.2/0340

9. DATE OF FIRST AUTHORISATION

18 April 2023

10. DATE OF REVISION OF THE TEXT

21 January 2025