Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE
NOMYSIS 2, 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
NOMYSIS 2 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 NOMYSIS 2 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 NOMYSIS 2 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
NOMYSIS 2 should not be used in the presence of any condition listed below. Should any of the conditions appear during the use of NOMYSIS 2, the use of NOMYSIS 2 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 NOMYSIS 2. If bleeding is heavy and continuous over time, this may lead to anaemia (severe in some cases). In the event of anaemia, discontinuation of NOMYSIS 2 should be considered.

Changes in menstrual bleeding pattern
The majority of patients treated with NOMYSIS 2 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 NOMYSIS 2 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 NOMYSIS 2.
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 NOMYSIS 2 (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 NOMYSIS 2.
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 NOMYSIS 2. 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 NOMYSIS 2.

Osteoporosis
Changes in bone mineral density (BMD).
The use of dienogest 2 mg (as in NOMYSIS 2) 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 NOMYSIS 2 because endogenous estrogen levels are moderately decreased during treatment with NOMYSIS 2.

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 NOMYSIS 2, 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 NOMYSIS 2.
- 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 NOMYSIS 2.
- 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 NOMYSIS 2.
- 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 NOMYSIS 2 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 NOMYSIS 2. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain.

Lactose
NOMYSIS 2 contains lactose (as lactose monohydrate):
- Patients with the rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take NOMYSIS 2.

4.5 Interactions with other medicines and other forms of interaction
Effects of other medicines on NOMYSIS 2
Individual enzyme-inducers or inhibitors (CYP3A4):
- Progestogens, including NOMYSIS 2, 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 NOMYSIS 2.
- An increased clearance of sex hormones due to enzyme induction may reduce the therapeutic effect of NOMYSIS 2 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 NOMYSIS 2 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 NOMYSIS 2 on other medicines
Based on *in vitro* inhibition studies, a clinically relevant interaction of NOMYSIS 2 with the cytochrome P450 enzyme mediated metabolism of other medicines is unlikely.

Other forms of interactions
The use NOMYSIS 2 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 NOMYSIS 2 during pregnancy is contraindicated (see section 4.3). If pregnancy occurs during the use of NOMYSIS 2, further intake should be stopped.

Breastfeeding
NOMYSIS 2 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 NOMYSIS 2. However, NOMYSIS 2 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 NOMYSIS 2.

4.7 Effects on ability to drive and use machines
NOMYSIS 2 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 NOMYSIS 2 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 NOMYSIS 2). 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 NOMYSIS 2) 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 NOMYSIS 2) 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 NOMYSIS 2 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
18 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
3 Gwen Lane, 4th Floor,
Sandton,
Gauteng,
2031.

8. REGISTRATION NUMBER
55/21.8.2/0897.896

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
01 August 2023

10. DATE OF REVISION OF THE TEXT
N.A

TRINITY PHARMA

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