APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

METRINELLE 2 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg Dienogest.

Excipients with known effect:

Contains sugar.

Each tablet contains 60,9 mg lactose monohydrate.

For the full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM

Tablets.

Round, biconvex, plain, white tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of endometriosis.

METRINELLE is indicated in the long-term treatment of endometriosis in adolescents after

menarche from 12 years of age onward and adults.

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 METRINELLE 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 METRINELLE 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 the next day to take the tablet at her usual time. A tablet not absorbed due to vomiting or diarrhoea should likewise be replaced by one tablet.

Special populations

Elderly population

There is no relevant indication for use of METRINELLE in the elderly population.

Patients with renal impairment

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

impairment.

Patients with hepatic impairment

METRINELLE is contraindicated in patients with present or past severe hepatic disease (see section 4.3).

Paediatric population

METRINELLE is not indicated in children prior to menarche. The efficacy of METRINELLE 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 METRINELLE 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 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.

Therefore, the treating medical practitioner should weigh the benefits of METRINELLE against the possible risks of use in each individual adolescent patient (see section 4.4).

Method of administration

For oral use.

4.3 Contraindications

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

- hypersensitivity to dienogest or to any of the excipients of METRINELLE (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
- history of or active venous thromboembolic disorder
- personal and family history of breast cancer
- previous proven deep-vein thrombosis (DVT)
- 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 METRINELLE 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 METRINELLE, although not all of the warnings and precautions are based on respective findings in the clinical studies with dienogest.

If any of the conditions/risk factors mentioned below is present or deteriorates, an individual risk-benefit analysis should be done before treatment with METRINELLE 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 METRINELLE. If bleeding is heavy and continuous over time, this may lead to anaemia (severe in some cases). In the event of anaemia, discontinuation of METRINELLE should be considered.

Changes in bleeding pattern

The majority of patients treated with METRINELLE 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 METRINELLE 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 METRINELLE.

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, such as METRINELLE. 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 early age), age, obesity, prolonged immobilisation, major surgery or major trauma. In case of long-term immobilisation, it is advisable to discontinue the use of METRINELLE (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

METRINELLE 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 METRINELLE 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.

Cases of benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of hormonal substances such as the one contained in METRINELLE. 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 METRINELLE.

Osteoporosis and changes in bone mineral density (BMD)

The use of dienogest in adolescents (12 to < 18 years) over a treatment period of 12 months was associated with a decrease in bone mineral density (BMD) in the lumbar spine (L2 - L4). After cessation of treatment, BMD increased towards pre-treatment levels over a period of 6

months in a subset of patients with decreased BMD.

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 METRINELLE because endogenous estrogen levels are moderately decreased during treatment with METRINELLE.
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

Depressed mood and depression are well-known undesirable effects of hormonal use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their medical practitioner in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

METRINELLE generally does not appear to affect blood pressure in normotensive women. However, if a sustained clinically significant hypertension develops during the use of METRINELLE, it is advisable to withdraw METRINELLE 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 METRINELLE.

METRINELLE 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 METRINELLE.
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 METRINELLE.

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

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

Lactose

METRINELLE contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take METRINELLE.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on METRINELLE

Individual enzyme-inducers or inhibitors (cytochrome P450 3A4 (CYP3A4))

Progestogens, including dienogest, as in METRINELLE, are metabolised mainly by CYP3A4 located both in the intestinal mucosa and in the liver. Therefore, inducers or inhibitors of CYP3A4 may affect the progestogen drug metabolism of METRINELLE.

An increased clearance of sex hormones due to enzyme induction may reduce the therapeutic effect of METRINELLE 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 therapeutic effects of METRINELLE 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 also oxcarbazepine, topiramate, felbamate, griseofulvin, nevirapine and products containing St John's wort (*Hypericum perforatum*)) that induces microsomal enzymes (e.g. cytochrome P450 enzymes) which can result in increased clearance of sex hormones.

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.

The effect of the CYP3A4 inducer rifampicin was studied in healthy postmenopausal women. Co-administration 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

When co-administered with sex hormones, many combinations of human immunodeficiency virus (HIV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with hepatitis C virus (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 with enzyme inhibiting properties

METRINELLE is a substrate of cytochrome CYP3A4.

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

Coadministration with the strong CYP3A4 enzyme inhibitor ketoconazole resulted in a 2,9-fold increase of AUC (0-24h) at steady state for dienogest. Concomitant administration of the moderate inhibitor erythromycin increased the AUC (0-24h) of dienogest at steady state by 1,6-fold.

Effects of METRINELLE on other medicines

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

Interaction with food

A standardised high fat meal did not affect the bioavailability of METRINELLE.

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 / fetal development, birth or development after birth for humans. However, METRINELLE should not be administered to pregnant women because there is no need to

treat endometriosis during pregnancy.

Breastfeeding

Treatment with METRINELLE 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 METRINELLE. However, METRINELLE is not a contraceptive.
If contraception is required a non-hormonal method should be used.
Based on available data, the menstrual cycle returns to normal within 2 months after cessation of treatment with METRINELLE.

4.7 Effects on ability to drive and use machines

It is not known if METRINELLE has an effect on the ability to drive or use machines. Caution is advised before driving a vehicle or operating machinery until the effects of METRINELLE are known.

4.8 Undesirable effects

Summary of the safety profile

Undesirable effects are more common during the first month after the start of treatment with METRINELLE and subside with continued treatment. There may be changes in bleeding pattern, such as spotting, irregular bleeding or amenorrhea. The most frequently reported

undesirable effects are headache, breast discomfort, depressed mood and acne.

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, mood altered
	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	*Less*	tinnitus

disorders	*frequent:*	
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 distension, vomiting
	Less frequent:	diarrhoea, constipation, abdominal discomfort, gastrointestinal inflammation, gingivitis
Skin and	*Frequent:*	acne, alopecia

subcutaneous tissue disorders		
	Less frequent:	dry skin, hyperhidrosis, pruritis, hirsutism, onychoclasis, dandruff, dermatitis, abnormal hair growth, photosensitivity reaction, pigmentation disorder
Musculoskeletal and connective tissue disorders	*Frequent:*	back pain
	Less frequent	bone pain, muscle spasms, 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 administration site conditions	*Frequent:*	asthenic conditions, irritability
	Less frequent	oedema.

Description of selected adverse events

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

A clinical trial with adolescent women (12 to < 18 years) reported a decrease in bone mineral density of the lumbar spine (L2 – L4) in 72 % of participants after 12 months of 2 mg dienogest 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 drug reactions to SAHPRA via the 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

Acute toxicity studies 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 – 30 mg dienogest per day (10 to 15 times higher dose than in METRINELLE) over 24 weeks of use was very well tolerated. However, overdosage may potentiate the adverse effects reported under section 4.8. 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: G03DB08.

Dienogest is a nortestosterone derivative with no androgenic but rather an 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 estradiol 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 decidualisation 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 single ingestion of a 2 mg tablet. Bioavailability is about 91 %. A standardised high fat meal did not affect the bioavailability of dienogest. The pharmacokinetics of dienogest are dose-proportional within the dose range of 1 to 8 mg.

Distribution

Dienogest is bound to serum albumin and does not bind to sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG). 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 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 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 – 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.

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 of METRINELLE can be predicted from single dose pharmacokinetics.

5.3 Preclinical safety data

No information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Magnesium stearate

Maize starch

Povidone K-30.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

PVC/PVDC and aluminium foil blister strips placed in an outer carton.

Pack size: 28 tablets.

6.6 Special precautions for disposal and other handling

None.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor Grapevine House,

Steenberg Office Park, Silverwood Close,

Westlake, 7945,

South Africa

8. REGISTRATION NUMBER

A51/21.8.2/0194

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 12 July 2022

10. DATE OF REVISION OF THE TEXT

21 January 2025