1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ROVULUM 2 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of ROVULUM contains 2 mg of dienogest.

Contains sugar: Lactose monohydrate 57,2 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

ROVULUM is a white, round, biconvex film-coated tablet embossed with "2" on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ROVULUM is indicated for the treatment of endometriosis.

ROVULUM 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

Adults

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 ROVULUM 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 ROVULUM 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

Paediatric

ROVULUM is not indicated in children prior to menarche. The efficacy of dienogest, as in ROVULUM has been demonstrated in the treatment of endometriosis – associated pelvic pain in adolescent patients (12 to18 years), with an overall favourable safety and tolerability profile.

The use of dienogest, as in ROVULUM 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 physician should weigh the benefits of ROVULUM against the possible risks of use in each individual adolescent patient (see section 4.4 and section 5.1).

Geriatric patients

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

Patients with hepatic impairment

ROVULUM 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.

Method of administration

For oral administration.

4.3. Contraindications

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

ROVULUM is contraindicated in:

- Patients with hypersensitivity to dienogest or to any excipients in ROVULUM (see section 6.1).
- Known or suspected pregnancy.
- Lactation.

- 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

Depressed mood, depression and the risk of suicidality

Depressed mood and depression are well-known undesirable effects of hormonal preparation 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. Patients who have a history of depression should be carefully observed and the medicine discontinued if the depression recurs to a serious degree.

General

Before starting ROVULUM 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.

Pregnancies that occur among users of progestogen-only preparations used for contraception (e.g. minipill) 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 ROVULUM should be decided on only after carefully weighing the benefits against the risks.

As ROVULUM is a progestogen-only preparation it can be assumed that warnings and special precautions for use of other progestogen-only preparations are also valid for the use of ROVULUM although not all of the warnings and precautions are based on respective findings in the clinical studies with dienogest, as in ROVULUM.

If any of the conditions/risk factors mentioned below is present or deteriorates, an individual risk-benefit analysis should be done before ROVULUM is started or continued.

Circulatory disorders

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 preparations like dienogest, as in ROVULUM. 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 ROVULUM (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 or suspicion of an arterial or venous thrombotic event.

Tumours

There is a risk of having breast cancer diagnosed in patients using dienogest, as in ROVULUM.

Cases of benign liver tumours and malignant liver tumours have been reported in users of hormonal medicines such as the one contained in ROVULUM. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages.

Changes in bleeding pattern

ROVULUM treatment affects the menstrual bleeding pattern in the majority of women (see section 4.8). Uterine bleeding, for example in women with adenomyosis uteri or uterine leiomyomata, may be aggravated with the use of ROVULUM. If bleeding is heavy and continuous over time this may lead to anaemia (severe in some cases). In the event of anaemia, discontinuation of ROVULUM should be considered.

Osteoporosis and changes in bone mineral density (BMD)

Currently, long-term data on BMD and risk of fractures in users of dienogest, as in ROVULUM are not available. Based on BMD assessed in adult patients before and after 6 months of treatment with dienogest, as in ROVULUM there was no reduction of mean BMD. In patients treated with leuprorelin acetate (LA), a mean reduction of 4, 04 % ± 4, 4 % was noted after the same period. In patients who are at an increased risk of osteoporosis a careful risk-benefit assessment should be performed before starting dienogest, as in ROVULUM because endogenous oestrogen levels are moderately decreased during treatment with dienogest.
The use of dienogest, as in Rovulum 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 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 (see section 4.4).
Therefore the treating medical practitioner should weigh the benefits of ROVULUM 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).

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

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

Other conditions

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

Insulin resistance and diabetes mellitus: ROVULUM 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 ROVULUM.

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

Ovarian cyst: Persistent ovarian follicle (often referred to as functional ovarian cyst) may occur during the use of ROVULUM. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain.

Chloasma

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

Medical examination

A complete medical history and physical and gynaecological examination should be taken prior to the initiation or reinstitution of ROVULUM, and should be repeated at least annually during the use of ROVULUM. 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.

Use in hepatic impairment

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

Use in renal impairment

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

Paediatric population

ROVULUM is not indicated in children prior to menarche.

Excipients

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

4.5. Interaction with other medicines and other forms of interaction

Effects of other medicines on ROVULUM:

Individual enzyme-inducers or inhibitors (CYP3A4):

Progestogens, including dienogest, as in ROVULUM, 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 medicine metabolism of ROVULUM.

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

Medicines increasing the clearance of sex hormones (diminished efficacy by enzyme-induction):

Interaction can occur with medicines (e.g. phenytoin, barbiturates, primidone, carbamazepine, rifampicin and possibly oxcarbazepine, topiramate, felbamate, griseofulvin, nevirapine and medicines containing St. John's wort) 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 not seen for 2 to 3 weeks but may then be sustained for at least 4 weeks after cessation of therapy.

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. The systemic exposure of dienogest at steady state, measured by AUC (0 – 24h), was decreased by 83 %.

Medicines with variable effects on the clearance of sex hormones

When co-administered with sex hormones, many HIV/HCV protease inhibitors (e.g. ritonavir, saquinavir, indinavir, nelfinavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine) can increase or decrease plasma concentrations of the progestogen. These changes may be clinically relevant in some cases.

Medicines with enzyme-inhibiting properties:

Dienogest is a substrate of cytochrome P450 (CYP) 3A4.

Strong and moderate CYP3A4 known CYP3A4 inhibitors like azole antifungals (e.g. ketoconazole, itraconazole, fluconazole, voriconazole), cimetidine, verapamil, macrolides (e.g. erythromycin, clarithromycin and roxithromycin), diltiazem, antidepressants (e.g. nefazodone, fluvoxamine, fluoxetine) and grapefruit juice may increase plasma levels of progestogens and result in undesirable effects.

Effects of ROVULUM on other medicines:

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

Other forms of interactions

Effects on 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. lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

Medicine food interactions

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

4.6. Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

If contraception is required a non-hormonal method should be used (e.g. condom). Based on available data, the menstrual cycle returns to normal within 2 months after cessation of treatment with ROVULUM.

Pregnancy

The administration of ROVULUM during pregnancy is contraindicated. If pregnancy occurs during the use of ROVULUM, further intake should be stopped.

Based on available data, ovulation is inhibited in the majority of patients during treatment with dienogest, as in ROVULUM. However, ROVULUM is not a contraceptive.

Breastfeeding

ROVULUM should not be used during lactation.

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

4.7. Effects on ability to drive and use machines

ROVULUM has no influence on 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 month after start of intake of dienogest, as in ROVULUM and subside with duration of treatment (see Section 4.4). The following undesirable effects have been reported in users of dienogest, as in ROVULUM.

The most frequently reported undesirable effects during treatment that were considered at least possibly related to, dienogest, as in ROVULUM were headache, breast discomfort, depressed mood and acne.

b) Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Blood and the lymphatic system disorders		Anaemia	
Metabolism and nutrition disorders	Increased weight	Decreased weight, increased appetite	
Psychiatric disorders	Depressed mood sleep disorder, nervousness, loss of libido, mood altered	Anxiety, Depression, mood swings	Depression as a well-known risk factor for suicidal behaviour and suicide
Nervous system disorders	Headache, migraine	Imbalance in autonomic nervous system, disturbance in attention	
Eye disorders		Dry eyes	
Ear and labyrinth disorders		Tinnitus	
Cardiac disorders		Unspecified circulatory system disorder, palpitations	
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders		Dyspnoea	
Gastrointestinal disorders	Nausea, abdominal pain, flatulence, abdominal distention, 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 spasm, pain in extremity, heaviness in extremities	
Renal and urinary disorders		Urinary tract infection	
Reproductive system and breast disorders	Breast discomfort, ovarian cyst, hot flush, uterine/vaginal bleeding including spotting	Vaginal candidiasis, vulvovaginal dryness, genital discharge, pelvic pain, atrophic vulvovaginitis, breast mass, fibrocystic breast diseases, breast induration,	
General disorders and administrative site conditions	Asthenic conditions, irritability	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.

Reporting of suspected adverse reactions

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 providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting From". Found online under SAHPRA's publications:

SAHPRA: https://www.sahpra.org.za/Publications/Index/8

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

Acute toxicity studies performed with dienogest, as in ROVULUM did not indicate a risk of acute adverse effects in case of inadvertent intake of a multiple of the daily therapeutic dose. 20 mg to 30 mg dienogest per day (10 to 15 times higher dose than in ROVULUM) over 24 weeks of use were very well tolerated. However, overdosage may potentiate the adverse effects reported under section 4.8.

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 estrogen

Pharmacotherapeutic group: Progestogens

ATC code: G03D

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 oestradiol on both the eutopic and ectopic endometrium. When given continuously, dienogest leads to a

hypoestrogenic, hypergestagenic endocrine environment and decidualisation of endometrial tissue.

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).

Endogenous estrogen 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 mean BMD. Currently, long-term data on bone mineral density (BMD) and risk of fractures in users of dienogest are not available.

In a 12-months study involving 103 adolescents the mean relative change in BMD of the lumbar spine (L2L4) from baseline was -1.2 %. In a subset of the patients with decreased BMD a follow-up measurement was performed 6 months after end of treatment and showed an increase in BMD to – 0, 6 %.

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 a 2 mg tablet. A standardised high fat meal did not affect the bioavailability of dienogest.

Bioavailability is about 91 %. 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 medicine is present as free steroid, 90 % is nonspecifically 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 mLl/ 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, can be predicted from single dose pharmacokinetics.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Cottonseed oil hydrogenated, hydroxypropylcellulose (E463), hypromellose (E464), lactose monohydrate, maize starch, magnesium stearate, povidone, sodium starch glycolate (type A), talc (E553b), titanium dioxide (E171).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 25 °C.

6.5. Nature and contents of container

ROVULUM is packed in PVC/PVDC/Aluminium blister strips. The blister strips are packed in printed cartons. Pack size of 28 film-coated tablets.

6.6. Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

52/21.8.2/0336

9. DATE OF FIRST AUTHORISATION

14 June 2022

10. DATE OF REVISION OF TEXT

29 August 2023

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

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