PROPOSED PROFESSIONAL INFORMATION FOR ENDOACT

SCHEDULING STATUS S3

1. NAME OF THE MEDICINE

ENDOACT 2 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg dienogest.

Contains sugar: each tablet contains 60,93 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Round plain white tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of endometriosis.

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

Tablets must be taken continuously 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 ENDOACT 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 a 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 ENDOACT in the elderly population.

Patients with hepatic impairment:

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

Patients with renal impairment:

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

Paediatric population:

ENDOACT is not indicated in children prior to menarche.

Method of administration

For oral use.

4.3 Contraindications

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

- Hypersensitivity to dienogest or to any of the excipients of ENDOACT listed in section 6.1;
- 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; see section 4.2
- 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 ENDOACT. If bleeding is heavy and continuous over time, this may lead to anaemia (severe in some cases). In the event of anaemia, discontinuation of ENDOACT should be considered.

Changes in bleeding pattern

The majority of patients treated with dienogest as contained in ENDOACT experience changes in their menstrual bleeding pattern (see section 4.8).

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 as in ENDOACT. 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 ENDOACT (in the case of elective surgery at least four weeks in advance) and not to resume treatment until two weeks after complete remobilisation.

Tumours

There is a risk of having breast cancer diagnosed in patients using ENDOACT.

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 ENDOACT. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages.

Osteoporosis

Changes in bone mineral density (BMD). The use of dienogest as contained in ENDOACT 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). The mean relative change in BMD from baseline to the end of treatment (EOT) was – 1,2 % with a range between -6 % and 5 % (IC 95 %: -1,70 % and -0,78 %. Repeated measurement at 6 months after the EOT in a subgroup with decreased BMD values showed a trend towards recovery. (Mean relative change from baseline: –2,3 % at EOT and -0,6 % at 6 months after EOT with a range between -9 % and 6 % (IC 95 %: -1,20 % and 0,06 %. 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 4.2.

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

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.

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

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

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

Therefore, in women with a history of extra-uterine pregnancy or an impairment of tube function, the use of ENDOACT should be decided 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.

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 ENDOACT.

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

Lactose

ENDOACT contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take ENDOACT.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on ENDOACT

Individual enzyme-inducers or inhibitors (CYP3A4)

Progestogens, including ENDOACT, 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 ENDOACT.

An increased clearance of sex hormones due to enzyme induction may reduce the therapeutic effect of ENDOACT 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 ENDOACT 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 induce microsomal enzymes (e.g. cytochrome P450 enzymes) which can result in increased clearance of sex hormones.

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 ENDOACT on other medicines

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

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 is 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 (see section 5.3).

However, ENDOACT should not be administered to pregnant women because there is no need to treat endometriosis during pregnancy.

Breastfeeding

Treatment with ENDOACT during lactation is not recommended. Physiochemical properties and animal data indicate excretion of dienogest in breastmilk.

Fertility

Based on the available data, ovulation is inhibited in the majority of patients during treatment with ENDOACT.

However, ENDOACT 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 ENDOACT.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive or use machines have been observed in users of products containing dienogest. However, patients should be advised to exercise caution until they know how ENDOACT affects them.

4.8 Undesirable effects

Summary of the safety profile

Undesirable effects are more common during the first months after the start of treatment with ENDOACT, and subside with continued treatment. There may be changes in bleeding pattern, such as spotting, irregular bleeding or amenorrhea. See section 4.4.

The most frequently reported undesirable effects under treatment with dienogest as contained in ENDOACT are headache, breast discomfort, depressed mood and acne.

Adverse reactions

Adverse reactions and their frequencies are reported in Table 1 by system organ class and by frequency.

Table 1: Tabulated summary of adverse reactions

The following undesirable effects have been reported.

System Organ Class	ENDOACT Tablets Side Effects
Blood and lymphatic system disorders	
Less frequent:	Anaemia
Metabolism and nutrition disorders	
Frequent:	Weight increase
Less frequent:	Weight decrease 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 eye
Ear and labyrinth disorders	
Less frequent:	Tinnitus
Cardiac disorders	
Less frequent:	Unspecific 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 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 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

Decrease of bone mineral density

In an uncontrolled clinical trial with 111 adolescent women (12 to <18 years) who were treated with dienogest as contained in ENDOACT, 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 of suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers 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 or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

Acute toxicity studies performed with dienogest as contained in ENDOACT 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 ENDOACT) over 24 weeks of use were very well tolerated. However, overdosage may potentiate the adverse effects reported in section 4.8. There is no specific antidote, treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 21.8.2 Progesterones with or without oestrogens

Pharmacotherapeutic group: progestogens; ATC code: G03DB08

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 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 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 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 ENDOACT can be predicted from single dose pharmacokinetics.

5.3 Preclinical safety data

Preclinical data reveal no special risks for humans based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. However, it should be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

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 in a cool, dry place.

Store in the original packaging to protect from light and moisture.

Store all medicines out of reach of children.

6.5 Nature and contents of container

The tablets are packed into blister packs consisting of clear to a slightly opaque film made of polyvinylidene chloride (PVDC) coated polyvinyl chloride (PVC), sealed onto push through aluminium foil (dull side lacquered, and bright side heat sealable lacquered).

Pack sizes: 2 X 14, 6 X 14, and 12 X 14 tablets.

Not all pack sizes may be marketed.

The blisters are contained in an outer cardboard carton.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER

50/21.8.2/0082

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 26 July 2022

Latest renewal: Not applicable

10. DATE OF REVISION OF THE TEXT

To be allocated