Approved Professional Information for Medicines for Human Use: ESDOPIL 3/0,03 mg

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ESDOPIL 3/0,03 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

21 pale yellow ESDOPIL 3/0,03 mg film-coated tablets

Each film-coated tablet contains 3 mg drospirenone and 0,03 mg ethinylestradiol.

7 white placebo film-coated tablets

The tablet does not contain active substances.

Contains sugar

Each ESDOPIL 3/0,03 mg film-coated tablet contains 70,17 mg lactose monohydrate.

Each placebo film-coated tablet contains 73,40 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

ESDOPIL 3/0,03 mg film-coated tablets

Pale yellow, cylindrical, biconvex, film-coated tablet with a diameter of approximately 6,00 mm.

Placebo film-coated tablets

White, cylindrical, biconvex, film-coated tablet with a diameter of approximately 6,00 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception

4.2 Posology and method of administration

Posology

How to start ESDOPIL 3/0,03 mg:

No preceding hormonal contraceptive use (in the past month):

Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). Starting on days 2 to 5 is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of tablet-taking.

Changing from a combined hormonal contraceptive (combined oral contraceptive), vaginal ring, or transdermal patch:

The woman should start with ESDOPIL preferably on the day after the last active tablet (the last tablet containing the active substances) of her

previous combined oral contraceptive, but at the latest on the day following the usual tablet-free or inactive tablet interval of her previous combined oral contraceptive. In case a vaginal ring or transdermal patch has been used, the woman should start using ESDOPIL preferably on the day of removal, but at the latest when the next application would have been due.

Changing from a progestogen-only method (minipill, injection, implant) or from a progestogen-releasing intrauterine system (IUS):

The woman may switch any day from the minipill, from an implant or the intrauterine system on the day of its removal and from an injectable when the next injection would be due, but should in all of these cases be advised to additionally use an additional barrier method for the first 7 days of tablet-taking.

Following first-trimester abortion:

The woman may start immediately. When doing so, she need not take additional contraceptive measures.

Following delivery or second-trimester abortion:

For breastfeeding women see section 4.6.

Women should be advised to start at day 21 to 28 after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of combined oral contraceptive use or the woman has to wait for her first menstrual period.

Management of missed tablets

Missed hormone-free white film-coated tablets can be disregarded. However, they should be discarded to avoid unintentionally prolonging the hormone-free white tablet phase. The following advice only refers to **missed hormone-containing pale-yellow** film-coated tablets:

If the user is ***less than 12 hours*** late in taking any active tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

If she is ***more than 12 hours*** late in taking any active tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

1. Active tablet-taking must never be discontinued for longer than 7 days;
2. 7 days of uninterrupted active tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Accordingly, the following advice can be given in daily practice:

First 7 days of active tablet-taking (Day 1 to 7):

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets that are missed and the closer they are to the inactive tablet phase, the higher the risk of a pregnancy.

Second 7 days of active tablet-taking (Day 8 to 14):

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

Third 7 days of active tablet-taking (Day 15 to 21):

The risk of reduced reliability is imminent because of the forthcoming inactive tablet phase. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. If either of the following two options is adhered to, there is no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, the woman should be advised to follow the first of these two options, and also to use extra precautions for the next 7 days.

1. The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time until the active tablets are used up. The 7 inactive tablets must be discarded. The next pack must be started right away. The user is unlikely to have a withdrawal bleed until the end of the active tablets section of the second pack, but she may experience spotting or breakthrough bleeding on active tablet-taking days.

2. The woman may also be advised to discontinue active tablet-taking from the current pack. She should then have a tablet-free interval of up to 7 days, including the days she missed tablets, and subsequently continue with the next pack, starting in the silver section with the tablet for the appropriate day of the week.

If the woman missed active tablets and subsequently has no withdrawal bleed in the inactive tablet phase, the possibility of a pregnancy should be considered.

Inactive tablet-taking:

The white tablets are inactive tablets and missing these can be disregarded. However, they should be discarded to avoid unintentionally prolonging the inactive tablet phase.

Advice in case of gastrointestinal disturbances

In case of severe gastrointestinal disturbances, absorption may not be complete and additional contraceptive measures should be taken.

If vomiting occurs within 3 to 4 hours after active tablet-taking, the advice concerning missed tablets is applicable. If the woman does not want to change her normal tablet-taking schedule, she must take the extra tablet(s) needed from another pack.

How to delay a period

To delay a period the woman should continue with another pack of ESDOPIL without taking the inactive tablets from her current pack. The extension can be carried on for as long as wished until the end of the active tablets in the second pack. During the extension the woman may

experience breakthrough bleeding or spotting. Regular intake of ESDOPIL is then resumed after the inactive tablet phase.

Special populations

Elderly population

Not applicable. ESDOPIL is not indicated after menopause.

Renal impairment

ESDOPIL is contra-indicated in women with severe renal insufficiency or acute renal failure. See also sections 4.3 and 5.2.

Hepatic impairment

ESDOPIL is contra-indicated in women with severe hepatic diseases. See also sections 4.3 and 5.2.

Paediatric population

ESDOPIL is only indicated after menarche. There are no data suggesting the need for a dosage adjustment.

Method of administration

Combined oral contraceptives, when taken correctly, have a failure rate of approximately 1 % per year. The failure rate may increase when pills are missed or taken incorrectly.

The first course of ESDOPIL is started on the first day of the menstrual period (day 1 of the cycle) from the silver section of the pack by selecting the appropriate tablet for that day of the week (e.g. "MON" for Monday). The tablet is swallowed whole with some liquid. Thereafter one tablet

must be taken daily for 28 days following the direction shown by the arrows. It does not matter at what time of the day the tablet is taken, but once the patient has selected a particular time, the tablet should be taken as near as possible at the same time each day. Withdrawal bleeding usually starts on day 2 to 3 after starting the inactive (hormone-free) tablets and may not have finished before the next pack is started. Each subsequent pack is started the day after the last tablet of the current pack. If a patient starts ESDOPIL during the latter part of the week, the very first cycle may be slightly shortened.

4.3 Contraindications

ESDOPIL should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during ESDOPIL use, the product should be stopped immediately.

- Hypersensitivity to drospirenone, ethinylestradiol or to any of the excipients listed in section 6.1.
- Hereditary or acquired predisposition for venous or arterial thrombosis, such as activated protein C resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia and antiphospholipid antibodies (anticardiolipin-antibodies, lupus anticoagulant).
- Presence or a history of venous or arterial thrombotic/thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction) or of a cerebrovascular accident. Presence or history of prodroma of a thrombosis (e.g. transient ischaemic attack, angina pectoris).

- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see section 4.4).
- History of migraine with focal neurological symptoms.
- Diabetes mellitus with vascular involvement.
- Severe hepatic disease as long as liver function values have not returned to normal.
- Severe renal insufficiency or acute renal failure with a creatinine clearance of less than 30 mL/minute.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Major surgery with prolonged immobilisation.

4.4 Special warnings and precautions for use

- If any of the conditions or risk factors mentioned below is present, the suitability of ESDOPIL should be discussed with the woman.
- In the event of aggravation, or first appearance of any of these conditions or risk factors, the woman should be advised to contact her doctor to determine whether the use of ESDOPIL should be discontinued.
- In case of suspected or confirmed VTE or ATE, CHC use should be discontinued. In case anticoagulant therapy is started, adequate

alternative contraception should be initiated because of the teratogenicity of anticoagulant therapy (coumarins).

- Circulatory Disorders

Risk of venous thromboembolism (VTE)

The use of any combined hormonal contraceptive (CHC) increases the risk of venous thromboembolism (VTE) compared with no use. Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. Other products such as ESDOPIL may have up to twice this level of risk. The decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with ESDOPIL, how her current risk factors influence this risk, and that her VTE risk is highest in the first ever year of use. There is also some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks or more.

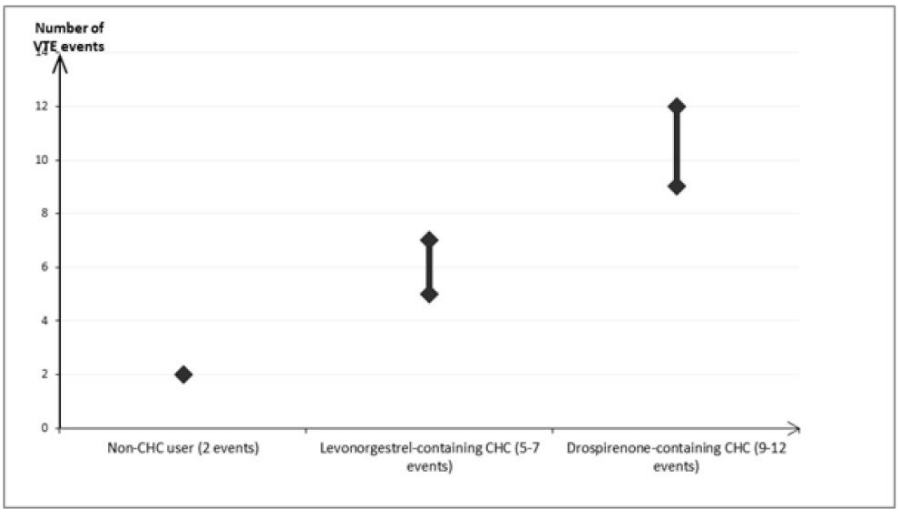
In women who do not use a CHC and are not pregnant, about 2 out of 10000 will develop a VTE over the period of one year. However, in any individual woman the risk may be far higher, depending on her underlying risk factors (see below).

It is estimated[1] that out of 10000 women who use a CHC containing drospirenone between 9 and 12 women will develop a VTE in one year; this compares with about 6[2] in women who use a levonorgestrel-containing CHC.

In both cases, the number of VTEs per year is fewer than the number expected during pregnancy or in the postpartum period.

VTE may be fatal in 1 – 2 % of the cases.

Figure: Number of VTE events per 10000 women in one year



Thrombosis has been reported to occur in CHC users in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries.

Risk factors for VTE

The risk for venous thromboembolic complications in CHC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see table).

ESDOPIL is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

Table: Risk factors for VTE

Risk factor	Comment

Obesity (body mass index over 30 kg/m^2)	Risk increases substantially as BMI rises. Particularly important to consider if other risk factors also present.
Prolonged immobilisation, major surgery, any surgery to the legs or pelvis; neurosurgery, or major trauma. Note: temporary immobilisation including air travel > 4 hours can also be a risk factor for VTE particularly in women with other risk factors.	In these situations, it is advisable to discontinue use of the pill (in the case of elective surgery at least four weeks in advance) and not resume until two after complete remobilisation. Another method of contraception should be sued to avoid unintentional pregnancy. Antithrombotic treatment should be considered if ESDOPIL has not been discontinued in advance.
Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use
Other medical conditions associated with VTE	Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease

Increasing age	Particularly above 35 years

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.

The increased risk of thromboembolism in pregnancy, and particularly the 6-week period of the puerperium, must be considered (see section 4.6).

Symptoms of VTE (deep vein thrombosis and pulmonary embolism)

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC as in ESDOPIL.

Symptoms of deep vein thrombosis (DVT) can include:

- unilateral swelling of the leg and/or foot or along a vein in the leg;
- pain or tenderness in the leg which may be felt only when standing or walking,
- increased warmth in the affected leg; red or discoloured skin on the leg.

Symptoms of pulmonary embolism (PE) can include:

- sudden onset of unexplained shortness of breath or rapid breathing;
- sudden coughing which may be associated with haemoptysis;
- sharp chest pain;
- severe light headedness or dizziness;
- rapid or irregular heartbeat.

Some of these symptoms (e.g. “shortness of breath”, “coughing”) are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discolouration of an extremity.

If the occlusion occurs in the eye symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

Risk of arterial thromboembolism (ATE)

Epidemiological studies have associated the use of CHCs with an increased risk for arterial thromboembolism (myocardial infarction) or for cerebrovascular accident (e.g. transient ischaemic attack, stroke). Arterial thromboembolic events may be fatal.

Risk factors for ATE

The risk of arterial thromboembolic complications or of a cerebrovascular accident in CHC users increases in women with risk factors (see table). ESDOPIL is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

Table: Risk factors for ATE

Risk factor	Comment
Increasing age	Particularly above 35 years
Smoking	Women should be advised not to smoke if they wish to use a CHC. Women over 35 who continue to smoke should be strongly advised to use a different method of contraception.
Obesity (body mass index over 30 kg/m^2)	Risk increases substantially as BMI increases. Particularly important in women with additional risk factors.
Positive family history (arterial thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.
Migraine	An increase in frequency or severity of migraine during CHC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation
Other medical conditions associated with adverse vascular events	Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus

Symptoms of ATE

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

Symptoms of a cerebrovascular accident can include:

- sudden numbness or weakness of the face, arm or leg, especially on one side of the body
- sudden trouble walking, dizziness, loss of balance or coordination
- sudden confusion, trouble speaking or understanding
- sudden trouble seeing in one or both eyes
- sudden, severe or prolonged headache with no known cause
- loss of consciousness or fainting with or without seizure.

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

Symptoms of myocardial infarction (MI) can include:

- pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone
- discomfort radiating to the back, jaw, throat, arm, stomach
- feeling of being full, having indigestion or choking
- sweating, nausea, vomiting or dizziness
- extreme weakness, anxiety, or shortness of breath
- rapid or irregular heartbeats.

Tumours

An increased risk of cervical cancer in long-term users of COCs (> 5 years) has been reported in some epidemiological studies, but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behaviour and other factors such as human papilloma virus (HPV).

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1,24) of having breast cancer diagnosed in women who are currently using COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

In some cases, benign liver tumours, and even malignant liver tumours have been reported in users of COCs. 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 COCs.

With the use of the higher-dosed COCs (50 µg ethinylestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to lower-dosed COCs remains to be confirmed.

Other conditions

The progestogen component in ESDOPIL is an aldosterone antagonist with potassium sparing properties. In most cases, no increase of potassium levels is to be expected. In a clinical study, however, in some patients with mild or moderate renal impairment and concomitant use of potassium-sparing medicines, serum potassium levels slightly, but not significantly, increased during drospirenone intake. Therefore, it is recommended to check serum potassium during the first treatment cycle in patients presenting with renal insufficiency and a pre-treatment serum potassium in the upper reference range, and particularly during concomitant use of potassium sparing medicines. See also section 4.5.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs as in ESDOPIL.

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. Only in these rare cases an immediate discontinuation of ESDOPIL use is justified. If, during the use of ESDOPIL in pre-existing hypertension, constantly elevated blood pressure values or a significant increase in blood pressure do not respond adequately to antihypertensive treatment, ESDOPIL must be withdrawn. Where considered appropriate, ESDOPIL use may be resumed if normotensive values can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with use of a COC, as in ESDOPIL, is inconclusive: jaundice and/or pruritus related to cholestasis; gallstones; porphyria; systemic lupus

erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

Acute or chronic disturbances of liver function may necessitate the discontinuation of ESDOPIL use until markers of liver function return to normal. Recurrence of cholestatic jaundice and/or cholestasis-related pruritus which previously occurred during pregnancy or during previous use of sex steroids necessitates the discontinuation of ESDOPIL.

Although ESDOPIL may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose ESDOPIL (containing < 0,05 mg ethinylestradiol). However, diabetic women should be carefully observed, particularly in the early stage of ESDOPIL use.

Worsening of epilepsy, of Crohn's disease and of ulcerative colitis has been reported during COC, as in ESDOPIL use.

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive 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 physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

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 COCs, as in ESDOPIL.

ALT elevations

During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicines containing ombitasvir / paritaprevir / ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs) (see sections 4.3 and 4.5).

Medical examination / consultation

Prior to the initiation or reinstitution of ESDOPIL a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and a physical examination should be performed, guided by the contraindications (see section 4.3) and warnings (see section 4.4). It is important to draw a woman's attention to the information on venous and arterial thrombosis, including the risk of ESDOPIL compared with other CHCs, the symptoms of VTE and ATE, the known risk factors and what to do in the event of a suspected thrombosis.

The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given. The frequency and nature of examinations should be based on established practice guidelines and be adapted to the individual woman.

Women should be advised that hormonal contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Reduced efficacy

The efficacy of COCs, as in ESDOPIL may be reduced in the event of e.g. missed tablets (see section 4.2), gastro-intestinal disturbances (see section 4.2) or concomitant medication (see section 4.5).

Reduced cycle control

With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles.

If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

In some women withdrawal bleeding may not occur during the tablet-free interval. If ESDOPIL has been taken according to the directions described in Section 4.2, it is unlikely that the woman is pregnant. However, if ESDOPIL has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before ESDOPIL use is continued.

Excipients: lactose intolerance

ESDOPIL 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

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

Effects of other medicines on ESDOPIL

Interactions can occur with medicines that induce microsomal enzymes and with some antibiotics which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure.

Management

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

Short-term treatment

Women on treatment with enzyme-inducing medicines should temporarily use a barrier method or another method of contraception in addition to ESDOPIL. The barrier method must be used during the whole time of the concomitant medicinal therapy and for 28 days after its discontinuation. If the medicinal therapy runs beyond the end of the tablets in ESDOPIL pack, the next ESDOPIL pack should be started right after the previous one without the usual tablet-free interval.

Long-term treatment

In women on long-term treatment with hepatic enzyme-inducing medicines, another reliable, non-hormonal, method of contraception is recommended.

The following interactions have been reported in the literature.

Medicines increasing the clearance of COCs (diminished efficacy of COCs by enzyme-induction), e.g.:

Barbiturates, bosentan, carbamazepine, phenytoin, primidone, rifampicin, and HIV medication ritonavir, nevirapine and efavirenz and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and products containing the herbal remedy St. John's Wort (*hypericum perforatum*).

Medicines with variable effects on the clearance of ESDOPIL:

When co-administered with COCs, as in ESDOPIL many combinations of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV inhibitors can increase or decrease plasma concentrations of estrogen or progestins. The net effect of these changes may be clinically relevant in some cases.

Therefore, the prescribing information of concomitant HIV/HCV medications should be consulted to identify potential interactions and any related recommendations. In case of any doubt, an additional barrier contraceptive method should be used by women on protease inhibitor or non-nucleoside reverse transcriptase inhibitor therapy.

Antibiotics (interference with enterohepatic circulation)

Some clinical reports suggest that enterohepatic circulation of estrogens may decrease when certain antibiotic medicines are given, which may reduce ethinylestradiol concentrations (e.g. penicillins, tetracyclines).

Medicines decreasing the clearance of ESDOPIL (enzyme inhibitors):

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

Concomitant administration of strong CYP3A4 inhibitors can increase plasma concentrations of the estrogen or the progestin or both.

In a multiple dose study with a drospirenone (3 mg/day) / ethinylestradiol (0,02 mg/day) combination, co-administration of the strong CYP3A4 inhibitor ketoconazole for 10 days increased the AUC(0-24h) of drospirenone and ethinylestradiol 2,7 fold and 1,4 fold respectively.

Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol 1,4 to 1,6-fold, respectively when taken concomitantly with a combined hormonal contraceptive containing 0,035 mg ethinylestradiol.

The main metabolites of drospirenone in human plasma are generated without involvement of the cytochrome P450 system. Inhibitors of this enzyme system are therefore unlikely to influence the metabolism of drospirenone.

Effect of ESDOPIL on other medicines

COCs may affect the metabolism of certain other medicines. Accordingly, plasma and tissue concentrations may either increase (e.g. ciclosporin) or decrease (e.g. lamotrigine).

Based on *in vivo* interaction studies in female volunteers using omeprazole, simvastatin or midazolam as marker substrate, a clinically relevant interaction of drospirenone at doses of 3 mg with the cytochrome P450 mediated metabolism of other medicines is unlikely.

Clinical data suggests that ethinylestradiol is inhibiting the clearance of CYP1A2 substrates leading to a weak (e.g. theophylline) or moderate (e.g. tizanidine) increase in their plasma concentration.

Pharmacodynamic interactions

Concomitant use with the medicines containing ombitasvir / paritaprevir / ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (see sections 4.3 and 4.4).

Therefore, ESDOPIL-users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with this combination medicine regimen. ESDOPIL can be restarted 2 weeks following completion of treatment with this combination medicine regimen.

In patients without renal insufficiency, the concomitant use of drospirenone and ACE-inhibitors or NSAIDs did not show a significant effect on serum potassium. Nevertheless, concomitant use of ESDOPIL with aldosterone antagonists or potassium-sparing diuretics has not been studied. In this case, serum potassium should be tested during the first treatment cycle. See also section 4.4.

Other forms of interaction

Laboratory tests

The use of contraceptive steroids 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. Drospirenone causes an increase in plasma renin activity and plasma aldosterone induced by its mild antimineralocorticoid activity.

4.6 Fertility, pregnancy and lactation

Pregnancy

ESDOPIL is not indicated during pregnancy.

If pregnancy occurs during use of ESDOPIL, the preparation should be withdrawn immediately.

The increased risk of VTE during the postpartum period should be considered when re-starting ESDOPIL (see section 4.2 and 4.4).

Breastfeeding

Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Therefore, the use of ESDOPIL should generally not be recommended until the breastfeeding mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk during ESDOPIL use. These amounts may affect the child.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. No effects on ability to drive and use machines have been observed in users of COCs, as in ESDOPIL.

4.8 Undesirable effects

a) Tabulated list of adverse reactions

System Organ Class	**Frequency**	
	Frequent	**Less Frequent**
Immune system disorders		hypersensitivity, asthma
Metabolism and nutrition disorders	weight increased	fluid retention, weight decreased
Psychiatric disorders	depressive mood, emotional lability, decreased and loss of libido	libido increased
Nervous system disorders	headache, migraine	
Eye disorders		contact lens intolerance
Ear and labyrinth disorders		hypoacusis
Vascular disorders		hypertension, hypotension, venous thromboembolism (VTE), arterial

		thromboembolism (ATE)
Gastrointestinal disorders	nausea, abdominal pain	vomiting, diarrhoea
Skin and subcutaneous tissue disorders		acne, eczema, pruritus, alopecia, erythema nodosum, erythema multiforme, rash, urticaria
Reproductive system and breast disorders	menstrual disorders, intermenstrual bleeding, breast pain, breast tenderness, vulvovaginal candidiasis	breast enlargement, vaginal infection, breast discharge, vaginal discharge

b) Description of selected adverse reactions

An increased risk of arterial and venous thrombotic and thrombo-embolic events, including myocardial infarction, stroke, transient ischaemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs, which are discussed in more detail in section 4.4. The following serious adverse events have been reported in women using COCs, which are discussed in section 4.4:

- Venous thromboembolic disorders;
- Arterial thromboembolic disorders;

- Hypertension;
- Liver tumours;
- Occurrence or deterioration of conditions for which association with COC use is not conclusive: Crohn's disease, ulcerative colitis, epilepsy, uterine myoma, porphyria, systemic lupus erythematosus, herpes gestationis, Sydenham's chorea, haemolytic uremic syndrome, cholestatic jaundice;
- Chloasma;
- Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal.
- In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

The frequency of diagnosis of breast cancer is very slightly increased among COC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown. For further information, see sections 4.3 and 4.4.

Interactions

Breakthrough bleeding and/or contraceptive failure may result from interactions of other medicines (enzyme inducers) with oral contraceptives (see section 4.5).

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

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za

4.9 Overdose

There has not yet been any experience of overdose with ESDOPIL. On the basis of general experience with combined oral contraceptives, symptoms that may possibly occur in this case are nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A 18.8 Ovulation controlling agents.

Pharmacotherapeutic group: Progestogens, fixed combinations
ATC Code: G03AA 12

The contraceptive effect of ESDOPIL is based on the interaction of various factors, the most important of which are seen as the inhibition of

ovulation and the changes in the cervical secretion. ESDOPIL is a combined oral contraceptive with ethinylestradiol and the progestogen drospirenone. In a therapeutic dosage, drospirenone also possesses antiandrogenic and mild antimineralocorticoid properties. It has no estrogenic, glucocorticoid and antiglucocorticoid activity.

There are indications from clinical studies that the mild antimineralocorticoid properties of drospirenone result in a mild antimineralocorticoid effect.

With the use of the higher dosed combined oral contraceptives (50 µg ethinylestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to lower dosed combined oral contraceptives remains to be confirmed.

5.2 Pharmacokinetic properties

Absorption

Drospirenone

Orally administered drospirenone is rapidly and almost completely absorbed. Peak serum concentrations of approximately 37 ng/mL are reached at about 1 to 2 hours after single ingestion. Bioavailability is about 76 to 85 %. Concomitant ingestion of food has no influence on bioavailability.

Ethinylestradiol

Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of about 54 to 100 pg/mL are reached within 1 to 2 hours. During absorption and first-liver passage, ethinylestradiol is

metabolised extensively, resulting in a mean oral bioavailability of about 45 % with a large interindividual variation of about 20 to 65 %. Concomitant intake of food reduced the bioavailability of ethinylestradiol in about 25 % of the investigated subjects while no change was observed in the others.

Distribution

Drospirenone

Drospirenone is bound to serum albumin and does not bind to sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG). Only 3 to 5 % of the total serum drug concentrations are present as free steroid, 95 to 97 % are non-specifically bound to albumin. The ethinylestradiol-induced increase in SHBG does not influence the serum protein binding of drospirenone. The apparent volume of distribution of drospirenone is about 3,7 to 4,2 l/kg.

Ethinylestradiol

Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98 %) and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 2,8 to 8,6 l/kg was determined.

Biotransformation

Drospirenone

Drospirenone is completely metabolised. The major metabolites in the plasma are the acid form of drospirenone, generated by opening of the lactone ring, and the 4,5-dihydro-drospirenone-3-sulphate, both of which

are formed without involvement of the P450 system. Drospirenone is metabolised to a minor extent by cytochrome P450 3A4 based on in vitro data. The clearance rate from serum is about 1,2 to 1,5 mL/min/kg. When drospirenone was acutely co-administered with ethinylestradiol, no direct interaction was found.

Ethinylestradiol

Ethinylestradiol is subject to pre-systemic conjugation in both the small bowel mucosa and the liver. Ethinylestradiol is primarily metabolised by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulphate. The clearance rate was reported to be about 2,3 to 7 mL/min/kg.

Elimination

Drospirenone

Drospirenone serum levels decrease in two phases. The terminal disposition phase is characterised by a half-life of approximately 31 hours. Drospirenone is not excreted in unchanged form. Its metabolites are excreted at a biliary to urinary ratio of about 1,2 to 1,4. The half-life of metabolite excretion with the urine and faeces is about 1,7 days.

Ethinylestradiol

Ethinylestradiol serum levels decrease in two disposition phases characterised by half-lives of about 1 hour and 10 to 20 hours, respectively. Unchanged medicine is not excreted, ethinylestradiol

metabolites are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 1 day.

Steady-state conditions

Drospirenone

Drospirenone pharmacokinetics are not influenced by SHBG levels. Following daily ingestion drug serum levels increase about two to threefold reaching steady-state conditions during the second half of a treatment cycle.

Ethinylestradiol

Steady-state conditions are reached during the second half of a treatment cycle when serum drug levels are higher by 40 to 110 % as compared to single dose.

Special population

Drospirenone

Effect of renal impairment:

Steady-state serum drospirenone levels in women with mild renal impairment (creatinine clearance CLcr, 50 to 80 mL/minute) were comparable to those of women with normal renal function (CLcr, > 80 mL/minute). The serum drospirenone levels were on average 37 % higher in women with moderate renal impairment (CLcr, 30 to 50 mL/minute) compared to those in women with normal renal function. Drospirenone treatment was well tolerated by all groups. Drospirenone treatment did not show any clinically significant effect on serum potassium concentration. Severe renal impairment was not studied.

Effect of hepatic impairment:

In women with moderate hepatic impairment (Child-Pugh B), mean serum drospirenone concentration time profiles were comparable to those of women with normal hepatic function during the absorption/distribution phases, with similar C_{max} values.

The mean terminal half-life of drospirenone for the volunteers with moderate hepatic impairment was about 1,8 times greater than for the volunteers with normal hepatic function.

An about 50 % decrease in apparent oral clearance (CL/f) was seen in volunteers with moderate hepatic impairment as compared to those with normal liver function. The observed decline in drospirenone clearance in volunteers with moderate hepatic impairment compared to normal volunteers did not translate into any apparent difference in terms of serum potassium concentrations between the two groups of volunteers.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Active film-coated tablets	Placebo film-coated tablets
Tablet core:	
Hydroxypropyl cellulose Lactose monohydrate Magnesium stearate Polacrilin potassium Sodium lauryl sulphate	Lactose monohydrate Magnesium stearate Polacrilin potassium Povidone Colloidal anhydrous silica
Film-coating:	

Opadry II Yellow 85F32771 Consisting of: Iron oxide yellow (E172) Polyethylene glycol / macrogol Polyvinyl alcohol Talc (E553b) Titanium dioxide (E171)	Opadry II White 85F18422 Consisting of: Polyethylene glycol / macrogol Polyvinyl alcohol 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 30 °C.

6.5 Nature and contents of container

ESDOPIL is packed in PVC / PVDC / Aluminium blisters. The blisters are subsequently packed into cardboard boxes.

Pack sizes: 28 tablets (21 active + 7 placebo)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

8. REGISTRATION NUMBER(S)

ESDOPIL 3/0,03 mg film-coated tablets: 55/18.8/0861

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 February 2024.

10. DATE OF REVISION OF THE TEXT