

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Drospirenone/ethinylestradiol 3mg/0.02mg film-coated tablets
Contrez

2. Qualitative and quantitative composition

24 light pink (active) film-coated tablets:

Each tablet contains 3 mg of drospirenone and 0.02 mg of ethinylestradiol.

Excipient with known effect in active tablet

Each tablet also contains 43.30 mg of lactose monohydrate. See section 4-4.

4 white placebo (inactive) film-coated tablets:

The tablet does not contain active substances.

Excipient with known effect in placebo tablet

Each tablet also contains 60 mg of lactose monohydrate. See section 4-4.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet.

Active: Light pink, circular, biconvex film-coated tablet with “D2” embossed on one side and plain on the other side.

Placebo: White, circular, biconvex film-coated tablet with “PC” embossed on one side and plain on the other side.

4. Clinical particulars

4.1 Therapeutic indications

- Oral contraception.
- Treatment of moderate acne vulgaris in women seeking oral contraception.
- Treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who have chosen oral contraception as their method of birth control.

4.2 Posology and method of administration

Posology

Tablets must be taken in the order directed on the package, at about the same time every day, with some liquid if needed. One tablet is taken daily for 28 days. Each subsequent pack is started the day after the last intake of the previous pack.

A withdrawal bleed usually starts on day 2 to 3 after starting placebo tablets (white tablets in the last row) and may not be finished before the next pack is started.

4.2.1 How to start drospirenone/ethinylestradiol

No preceding hormonal contraceptive use (in the past month)

Tablet-taking has to start on day 1 of the patient's natural cycle (i.e., the first day of her menstrual bleeding). Starting on day 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 (COC), vaginal ring or transdermal patch)

The patient should start with drospirenone/ethinylestradiol preferably on the day after the last active tablet (the last tablet containing the active substances) of her previous COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC. In case a vaginal ring or transdermal patch has been used the woman should start using drospirenone/ethinylestradiol preferably on the day of removal, but at the latest when the next application would have been due.

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

The patient may switch any day from the progestogen-only pill (from an implant or the IUS on the day of its removal, from an injectable when the next injection would be due) but should in all of these cases be advised to additionally use a barrier method for the first 7 days of tablet-taking.

Following first-trimester abortion

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

Following delivery or second-trimester abortion

Patients 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. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of drospirenone/ethinylestradiol use or the woman has to wait for her first menstrual period.

4.2.2 Management of missed tablets

Advice in case of missed pills

Placebo tablets from the last (4th) row of the blister can be disregarded. However, they should be discarded to avoid unintentionally prolonging the placebo tablet phase.

The following advice only refers to **missed active tablets**:

If the user is **less than 12 hours** late in taking any 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 tablet, contraceptive protection may be reduced.

The management of missed tablets can be guided by the following two basic rules:

1. The recommended hormone-free tablet interval is 4 days, tablet-taking must never be discontinued for longer than 4 days.

2. 7 days of uninterrupted tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

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

Day 1-7

The user should take the last missed tablet as soon as they remember, 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 are missed and the closer they are to the placebo tablet phase, the higher the risk of pregnancy.

Day 8-14

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 she has missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

Day 15-24

The risk of reduced reliability is imminent because of the forthcoming placebo tablet phase. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore 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, she should follow the first of these two options and use extra precautions for the next 7 days as well.

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 4 placebo tablets from the last row must be discarded. The next blister 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 tablet-taking days.
2. The woman may also be advised to discontinue active tablet-taking from the current blister pack. She should then take placebo tablets from the last row for up to 4 days, including the days she missed tablets, and subsequently continue with the next blister pack.

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

Advice in case of gastro-intestinal disturbances

In case of severe gastrointestinal disturbance (e.g., vomiting or diarrhoea), absorption may not be complete and additional contraceptive measures should be taken. Unless diarrhoea is extremely severe, it does not affect steroidal absorption.

If vomiting occurs within 3-4 hours after active tablet taking, a new (replacement) tablet should be taken as soon as possible. The new tablet should be taken within 24 hours of the usual time of

tablet-taking if possible. If more than 24 hours elapse, the advice concerning missed tablets, as given in section 4.2 “Management of missed tablets”, is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) from another blister pack.

4.2.4 How to postpone a withdrawal bleed

To delay a period the woman should continue with another blister pack of drospirenone/ethinylestradiol without taking the placebo 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 drospirenone/ethinylestradiol is then resumed after the placebo tablet phase.

To shift her periods to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming placebo tablet phase by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough bleeding and spotting during the subsequent pack (just as when delaying a period).

4.2.5 Additional information on special populations

Based on epidemiological data collected on more than 2000 adolescent women aged below 18 years, there is no data indicating that safety and efficacy in this young age group is different from that known in women aged above 18 years.

Paediatric population

Drospirenone/ethinylestradiol is only indicated after menarche.

Elderly

Drospirenone/ethinylestradiol is not indicated after menopause.

Patients with hepatic impairment

Drospirenone/ethinylestradiol is contraindicated in women with severe hepatic diseases. See also sections 4.3 and 5.2.

Patients with renal impairment

Drospirenone/ethinylestradiol is contraindicated in women with severe renal insufficiency or acute renal failure. See also sections 4.3 and 5.2.

4.3 Contraindications

Combined oral contraceptives 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 use, the product should be stopped immediately.

- Presence or risk of venous thromboembolism (VTE)
- Venous thromboembolism – current VTE (on anticoagulants) or history of (e.g., deep venous thrombosis [DVT] or pulmonary embolism [PE]).
- Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance, (including Factor V Leiden), antithrombin-III deficiency, protein C deficiency, and protein S deficiency.

- Major surgery with prolonged immobilisation (see section 4.4).
- A high risk of venous thromboembolism due to the presence of multiple risk factors (see section 4.4)
- Presence or risk of arterial thromboembolism (ATE)
- Arterial thromboembolism – current arterial thromboembolism, history of arterial thromboembolism (e.g., myocardial infarction) or prodromal condition (e.g., angina pectoris)
- Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g., transient ischaemic attack and TIA).
- Known hereditary or acquired predisposition for arterial thromboembolism, such as anticoagulant).
- History of migraine with focal neurological symptoms.
- A high risk of arterial thromboembolism due to multiple risk factors (see section 4.4) or to the presence of one serious risk factor such as:
diabetes mellitus with vascular symptoms
severe hypertension
severe dyslipoproteinaemia
- Pancreatitis or a history thereof is associated with severe hypertriglyceridaemia.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Severe renal insufficiency or acute renal failure with a creatine clearance of < 30 mL/min.
- 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.
- Hypersensitivity to the active substances or any of the excipients listed in section 6.1.
- Drospirenone/ethinylestradiol is contraindicated for concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir (see section 4.5).

4.4 Special warnings and precautions for use

Warnings

If any of the conditions or risk factors mentioned below is present, the suitability of drospirenone/ethinylestradiol should be discussed with the woman. In the event of aggravation, the 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 drospirenone/ethinylestradiol 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

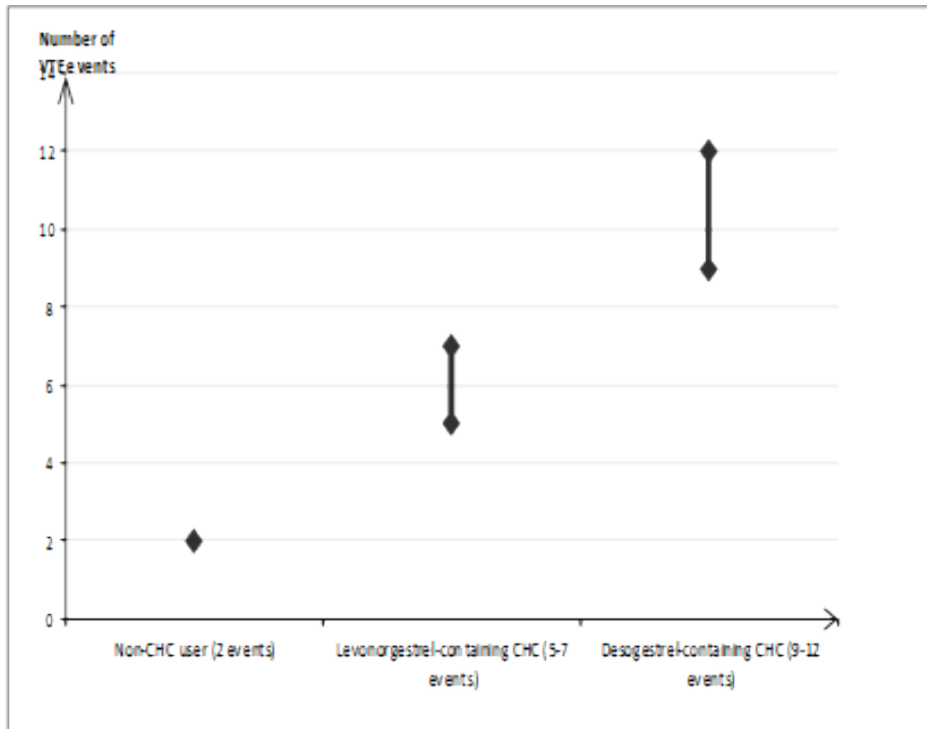
Risk of venous thromboembolism (VTE)

- 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 drospirenone/ethinylestradiol 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 drospirenone/ethinylestradiol, 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 10,000 will develop a VTE over one year. However, in any individual woman, the risk may be far higher depending on her underlying risk factors (see below). It is estimated¹ that out of 10,000 women who use a CHC containing drospirenone between 9 and 12 women will develop a VTE in one year; this compares with about 6² 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 cases.

Number of VTE events per 10,000 women in one year



Extremely rarely, 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). Drospirenone/ethinylestradiol 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, the increase in risk may be 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 are also present.
Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma	In these situations, it is advisable to discontinue the use of the patch/pill/ring (in the case of elective surgery at least four weeks in advance) and not resume until two
Note: Temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors.	weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if drospirenone/ethinylestradiol 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 (for information on “Pregnancy and lactation” 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.

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 lightheadedness or dizziness.
- rapid or irregular heartbeat.

Some of these symptoms (e.g., "shortness of breath", and "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 discoloration 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 cerebrovascular accident (e.g., transient ischaemic attack and stroke). Arterial thromboembolic events may be fatal.

Risk factors for ATE

The risk of arterial thromboembolic complications or a cerebrovascular accident in CHC users increases in women with risk factors (see table). Drospirenone/ethinylestradiol is contraindicated if a woman has one serious or multiple risk factors for ATE that put her at high risk of arterial thrombosis (see section 4.3). If a woman has more than one risk factor, the increase in risk may be 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.
Hypertension	
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., below 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 and 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 a seizure.

Temporary symptoms suggest the event is a transient ischaemic attack (TIA). Symptoms of myocardial infarction (MI) can include:

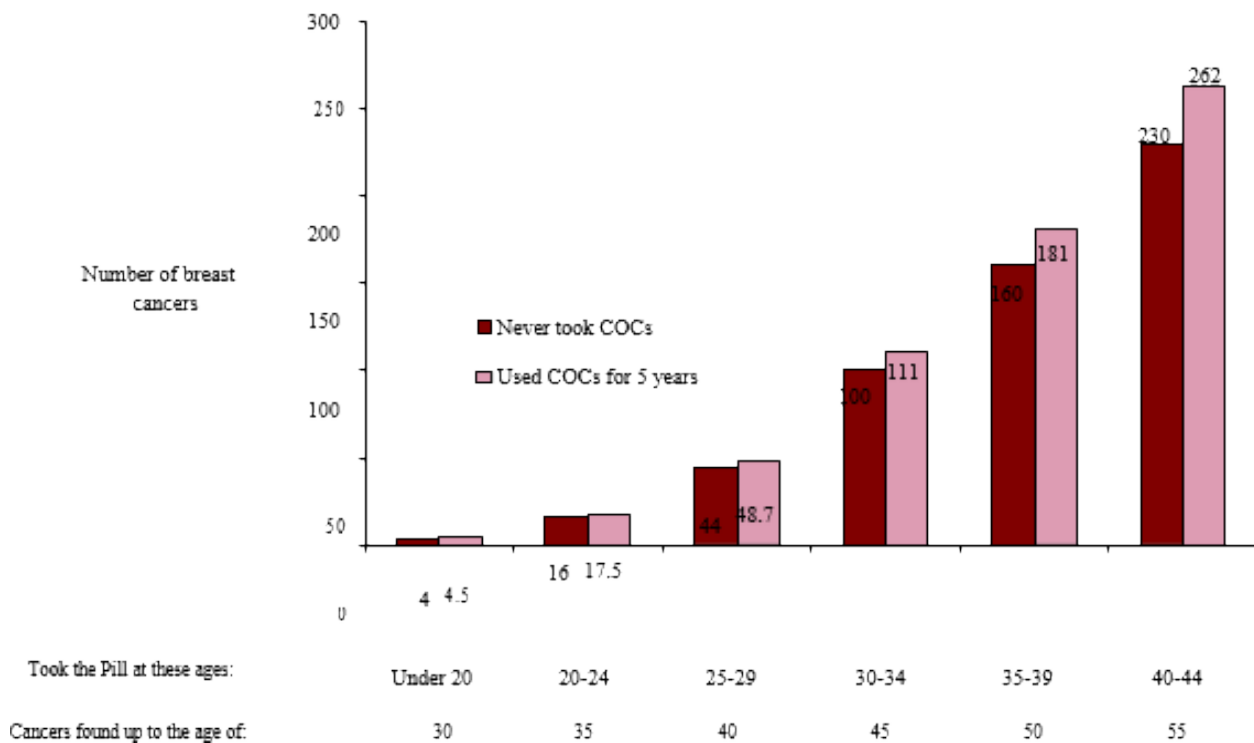
- pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone.
- discomfort radiating to the back, jaw, throat, arm and stomach.
- the feeling of being full, having indigestion or choking.
- sweating, nausea, vomiting or dizziness.
- extreme weakness,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

Tumours

- An increased risk of cervical cancer in long-term users of combined oral contraceptives has been reported in some studies, but there continues to be controversy about the extent to which this is attributable to the confounding effects of sexual behaviour and other factors such as the 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 combined oral contraceptives (COCs). 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 additional breast cancers diagnosed in current users of COCs or in women who have used COCs in the last ten years are more likely to be localised to the breast than those in women who never used COCs.
- Breast cancer is rare among women under 40 years of age whether or not they take COCs. Whilst this background risk increases with age, the excess number of breast cancer diagnoses in current and recent COC users is small with the overall risk of breast cancer (see bar chart).

- The most important risk factor for breast cancer in COC users is the age women discontinue the COC; the older the age at stopping, the more breast cancers are diagnosed. Duration of use is less important and the excess risk gradually disappears during the course of the 10 years after stopping COC use such that by 10 years there appears to be no excess.
- The possible increase in risk of breast cancer should be discussed with the user and weighed against the benefits of COCs taking into account the evidence that they offer substantial protection against the risk of developing certain other cancers (e.g., ovarian and endometrial cancer).
- In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of CHCs. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when upper abdominal pain, enlarged liver or signs of intra-abdominal haemorrhage occur in women taking CHCs.

Estimated cumulative numbers of breast cancers per 10,000 women diagnosed in 5 years of use and up to 10 years after stopping COCs, compared with numbers of breast cancers diagnosed in 10,000 women who had never used COCs



Other conditions

- Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using CHCs.
- Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.
- Although small increases in blood pressure have been reported in many women taking CHCs, clinically relevant increases are rare. A relationship between CHC use and clinical hypertension

has not been established. However, if a sustained clinically significant hypertension develops during the use of a CHC then it is prudent for the physician to withdraw the CHC and treat the hypertension. Where considered appropriate, CHC 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 CHC use, but the evidence of an association with CHC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.
- Acute or chronic disturbances of liver function may necessitate the discontinuation of CHC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred previously during pregnancy or use of sex steroids necessitates the discontinuation of CHCs.
- Although CHCs may affect peripheral insulin resistance and glucose tolerance, there is no evidence of a need to alter the therapeutic regimen in diabetics using CHCs. However, diabetic women should be carefully observed while taking CHCs.
- Crohn's disease and ulcerative colitis have been associated with CHC use.
- 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 this preparation.

Relative Contraindications

Severe depression or a history of this condition. 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.

4.4.1 Medical Examination/Consultation

Prior to the initiation or reinstatement of drospirenone/ethinylestradiol, 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 drospirenone/ethinylestradiol 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. If there is a risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method.

4.4.2 Reduced Efficacy

The efficacy of drospirenone/ethinylestradiol may be reduced in the event of missed tablets (Section 4.2.3), gastrointestinal disturbances (Section 4.2.4) or concomitant medications that decrease the plasma concentration of etonogestrel, the active metabolite of drospirenone (Section

4.5.1).

4.4.3 Reduced Cycle Control/ irregular bleeding

With all CHCs, 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 the CHC has been taken according to the directions described in Section 4.2, it is unlikely that the woman is pregnant. However, if the CHC has not been taken according to these directions before the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before CHC use is continued.

¹ These incidences were estimated from the totality of the epidemiological study data, using relative risks for the different products compared with levonorgestrel-containing CHCs.

² Mid-point of range of 5-7 per 10,000 WY, based on relative risk for CHCs containing levonorgestrel versus non-use of approximately 2.3 to 3.6.

Excipients

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

The small amount of lactose in this medicine is unlikely to cause symptoms in patients with lactose intolerance.

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Interactions

Interactions between oral contraceptives and other medicinal products 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 drug therapy enzyme induction may be sustained for about 4 weeks.

Short-term treatment

Women on treatment with enzyme-inducing drugs should temporarily use a barrier method or another method of contraception in addition to the COC. The barrier method must be used during the whole time of the concomitant drug therapy and for 28 days after its discontinuation. If the drug therapy runs beyond the end of the active tablets in the COC pack, the placebo tablets must be discarded and the next COC pack should be started right away.

Long-term treatment

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

The following interactions have been reported in the literature:

Substances increasing the clearance of COCs (diminished efficacy of COCs by enzyme induction)

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*).

Substances with variable effects on the clearance of COCs

When co-administered with COCs 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.

Substances decreasing the clearance of COCs (enzyme inhibitors)

The clinical relevance of potential interactions with enzyme inhibitors remains unknown. Concomitant administration of strong CYP3A4 inhibitors can increase plasma concentrations of estrogen or progestin or both. In a multiple-dose study with 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.

Effects of drospirenone/ethinylestradiol on other medicinal products

COCs may affect the metabolism of certain other active substances. 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, an interaction of drospirenone at doses of 3 mg with the cytochrome P450 mediated metabolism of other active substances 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

During clinical trials with patients treated for hepatitis C virus infections, (HCV) with medicinal products 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). Additionally, in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs (see sections 4.3).

Therefore, drospirenone/ethinylestradiol-users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with these combination drug regimens. Drospirenone/ethinylestradiol can be restarted 2

weeks following completion of treatment with these combination drug regimens. 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, the concomitant use of drospirenone/ethinylestradiol 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.

4.5.2 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

Drospirenone/ethinylestradiol is not indicated for use during pregnancy. If pregnancy occurs during treatment with drospirenone/ethinylestradiol, further intake should be stopped. Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs before pregnancy nor a teratogenic effect when COCs were taken inadvertently during pregnancy. Animal studies have shown undesirable effects during pregnancy and lactation (see section 5.3). Based on these animal data, undesirable effects due to the hormonal action of the active compounds cannot be excluded. However, general experience with COCs during pregnancy did not provide evidence for an actual adverse effect in humans.

The available data regarding the use of drospirenone/ethinylestradiol during pregnancy are too limited to permit conclusions concerning the negative effects of drospirenone/ethinylestradiol on pregnancy, the health of the foetus or neonate. To date, no relevant epidemiological data are available. The increased risk of VTE during the postpartum period should be considered when re-starting drospirenone/ethinylestradiol (see sections 4.2 and 4.4).

Breastfeeding

Lactation may be influenced by CHCs as they may reduce the quantity and change the composition of breast milk. Therefore, the use of CHCs should generally not be recommended until the nursing mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk but there is no evidence that this adversely affects infant health.

Fertility

Drospirenone/ethinylestradiol is indicated for the prevention of pregnancy.

4.7 Effects on the ability to drive and use machines

No effects on the ability to drive and use machines have been observed.

4.8 Undesirable effects

The table below reports adverse reactions by MedDRA system organ classes (MedDRA SOCs). The frequencies are based on clinical trial data. The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Adverse drug reactions which have been associated with the use of drospirenone/ethinylestradiol as oral contraceptive or in the treatment of moderate acne vulgaris according to the MedDRA system organ classes and MedDRA terms. All ADRs are listed by system organ class and frequency; common ($\geq 1/100$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($< 1/1,000$) and not known (cannot be estimated from the available data).

System Organ Class (MedDRA version 9.1)	common ($\geq 1/100$ to $< 1/10$)	uncommon ($\geq 1/1,000$ to $< 1/100$)	rare ($\geq 1/10,000$ to $< 1/1,000$)	not known (cannot be estimated from the available data)
Infections and infestations			Candidiasis	
Blood and lymphatic system disorders			Anemia Thrombocythemia	
Immune system disorders			Allergic reaction	Hypersensitivity
Endocrine disorders			Endocrine disorder	
Metabolism and nutrition disorders			Increased appetite Anorexia Hyperkalemia Hyponatremia	
Psychiatric disorders	Emotional lability	Depression Nervousness Somnolence	Anorgasmia Insomnia	
Nervous system disorders	Headache	Dizziness Paresthesia	Vertigo Tremor	
Eye disorders			Conjunctivitis Dry eye Eye disorder	
Cardiac disorders			Tachycardia	
Vascular disorders		Migraine Varicose vein Hypertension	Phlebitis Vascular disorder Epistaxis Syncope	

			Venous thromboembolism (VTE) Arterial thromboembolism (ATE)	
Gastrointestinal disorders	Nausea	Abdominal pain Vomiting Dyspepsia Flatulence Gastritis Diarrhea	Abdomen enlarged Gastrointestinal disorder Gastrointestinal fullness Hiatus hernia Oral candidiasis Constipation Dry mouth	
Hepatobiliary disorders			Biliary pain Cholecystitis	
Skin and subcutaneous tissue disorders		Acne Pruritus Rash	Chloasma Eczema Alopecia Dermatitis acneiform Dry skin Erythema nodosum Hypertrichosis Skin disorder Skin striae Contact dermatitis Photosensitive dermatitis Skin nodule	Erythema multiforme
Musculoskeletal and connective tissue disorders		Back pain Pain in extremity Muscle cramps		
Reproductive system and breast disorders	Breast pain Metrorrhagia* Amenorrhea	Vaginal candidiasis Pelvic pain Breast enlargement Fibrocystic breast Uterine / Vaginal bleeding* Genital discharge Hot flushes Vaginitis Menstrual disorder Dysmenorrhea Hypomenorrhea Menorrhagia	Dyspareunia Vulvovaginitis Postcoital bleeding Withdrawal bleeding Breast cyst Breast hyperplasia Breast neoplasm Cervical polyp Endometrial atrophy Ovarian cyst Uterine enlargement	

		Vaginal dryness Papanicolaou smear suspicious Libido decreased		
General disorders and administration site conditions		Asthenia Sweating increased Oedema (Generalized oedema, Peripheral oedema, Face oedema)	Malaise	
Investigations		Weight increase	Weight decrease	

* bleeding irregularities usually subside during continued treatment

Interactions

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Adverse Drug Reaction (ADR)/ Serious Adverse Event (SAE) electronic form linked to the MCAZ database using the following link: <https://primaryreporting.who-umc.org/ZW>.

4.9 Overdose

There has not yet been any experience of overdose with drospirenone/ethinylestradiol. Based on general experience with combined oral contraceptives, symptoms that may occur in the case of taking an overdose of active tablets are nausea, vomiting and withdrawal bleeding. Withdrawal bleeding may even occur in girls before their menarche if they accidentally take the medicinal product. There are no antidotes and further treatment should be symptomatic.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacological classification: 21.2.1 Combined oral contraceptives.

Drospirenone/ethinylestradiol 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 antigluco-corticoid activity. This gives drospirenone a pharmacological profile closely resembling the natural hormone progesterone. There are indications from clinical studies that the mild antimineralocorticoid properties of drospirenone/ethinylestradiol result in a mild antimineralocorticoid effect.

Two multicenter, double-blind, randomized, placebo-controlled studies were performed to evaluate the efficacy and safety of drospirenone/ethinylestradiol in women with moderate acne vulgaris. After six months of treatment, in comparison with placebo, drospirenone/ethinylestradiol showed a

statistically significantly greater reduction of 15.6 % (49.3% versus 33.7%) in inflammatory lesions, 18.5% (40.6% versus 22.1%) in non-inflammatory lesions, and 16.5% (44.6% versus 28.1%) in total lesion counts. In addition, a higher percentage of subjects 11.8% (18.6% versus 6.8%) showed a 'clear' or 'almost clear' rating on the Investigator's Static Global Assessment (ISGA) scale.

5.2 Pharmacokinetic properties

Drospirenone

Absorption

Orally administered drospirenone is rapidly and almost completely absorbed. Maximum concentrations of the active substance in the serum of about 38 ng/ml are reached at about 1-2 h after a single ingestion. Bioavailability is between 76 and 85 %. Concomitant ingestion of food does not influence the bioavailability of drospirenone.

Distribution

After oral administration, serum drospirenone levels decrease with a terminal half-life of 31 h. Drospirenone is bound to serum albumin and does not bind to sex hormone-binding globulin (SHBG) or corticoid-binding globulin (CBG). Only 3 - 5 % of the total serum concentrations of the active substance are present as free steroids. The ethinylestradiol-induced increase in SHBG does not influence the serum protein binding of drospirenone. The mean apparent volume of distribution of drospirenone is 3.7 ± 1.2 l/kg.

Biotransformation

Drospirenone is extensively metabolized after oral administration. The major metabolites in plasma are the acid form of drospirenone, generated by the opening of the lactone ring, and the 4,5-dihydro-drospirenone-3-sulfate, formed by reduction and subsequent sulfation. Drospirenone is also subject to oxidative metabolism catalyzed by CYP3A4.

In vitro, drospirenone is capable to inhibit weakly to moderately the cytochrome P450 enzymes CYP1A1, CYP2C9, CYP2C19 and CYP3A4.

Elimination

The metabolic clearance rate of drospirenone in serum is 1.5 ± 0.2 ml/min/kg. Drospirenone is excreted only in trace amounts in unchanged form. The metabolites of drospirenone are excreted with the faeces and urine at an excretion ratio of about 1.2 to 1.4. The half-life of metabolite excretion with the urine and faeces is about 40 h.

Steady-state conditions

During a treatment cycle, maximum steady-state concentrations of drospirenone in serum of about 70 ng/ml are reached after about 8 days of treatment. Serum drospirenone levels accumulated by a factor of about 3 as a consequence of the ratio of terminal half-life and dosing interval.

Steady-state conditions in special populations

Effect of renal impairment

Steady-state serum drospirenone levels in women with mild renal impairment (creatinine clearance CL_{cr}, 50-80 mL/min) were comparable to those of women with normal renal function. The serum drospirenone levels were on average 37 % higher in women with moderate renal impairment (CL_{cr}, 30 - 50 mL/min) compared to those in women with normal renal function. Drospirenone treatment was also well tolerated by women with mild and moderate renal impairment. Drospirenone treatment did not show any clinically significant effect on serum potassium concentration.

Effect of hepatic impairment

In a single-dose study, oral clearance (CL/F) was decreased by approximately 50 % 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 did not translate into any apparent difference in terms of serum potassium concentrations. Even in the presence of diabetes and concomitant treatment with spironolactone (two factors that can predispose a patient to hyperkalemia) an increase in serum potassium concentrations above the upper limit of the normal range was not observed. It can be concluded that drospirenone is well tolerated in patients with mild or moderate hepatic impairment (Child-Pugh B).

Ethnic groups

No clinically relevant differences in the pharmacokinetics of drospirenone or ethinylestradiol between Japanese and Caucasian women have been observed.

Ethinylestradiol

Absorption

Orally administered ethinylestradiol is absorbed rapidly and completely. Peak serum concentrations of about 33 pg/ml are reached within 1-2 hours after single oral administration. Absolute bioavailability as a result of presystemic conjugation and first-pass metabolism is approximately 60 %. 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

Serum ethinylestradiol levels decrease in two phases, the terminal disposition phase is characterized by a half-life of approximately 24 hours. Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98.5 %) and induces an increase in the serum concentrations of SHBG and corticoid-binding globulin (CBG). An apparent volume of distribution of about 5 l/kg was determined.

Biotransformation

Ethinylestradiol is subject to significant gut and hepatic first-pass metabolism. Ethinylestradiol is primarily metabolized 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 sulfate. The metabolic clearance rate of ethinylestradiol is about 5 ml/min/kg.

In vitro, ethinylestradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism-based inhibitor of CYP3A4/5, CYP2C8 and CYP2J2.

Elimination

Ethinylestradiol is not excreted in unchanged form to any significant extent. The metabolites of ethinylestradiol are excreted at a urinary-to-biliary ratio of 4:6. The half-life of metabolite excretion is about 1 day. The elimination half-life is 20 hours.

Steady-state conditions

Steady-state conditions are reached during the second half of a treatment cycle and serum levels of ethinylestradiol accumulate by a factor of about 2.0 to 2.3.

5.3 Preclinical safety data

In laboratory animals, the effects of drospirenone and ethinylestradiol were confined to those associated with the recognised pharmacological action. In particular, reproduction toxicity studies revealed embryotoxic and fetotoxic effects in animals which are considered species-specific. At exposures exceeding those in users of drospirenone/ethinylestradiol, effects on sexual differentiation were observed in rat foetuses but not in monkeys. Environmental risk assessment studies have shown that ethinylestradiol and drospirenone have the potential of posing a risk to the aquatic environment (see section 6.6).

6. Pharmaceutical particulars

6.1 List of excipients

Active tablet

Tablet core

Lactose monohydrate
Pregelatinised starch
Maize starch
Croscarmellose sodium
Povidone
Magnesium stearate

Film coat

Opadry Pink

Placebo tablet

Tablet core

Lactose monohydrate
Pregelatinised starch
Magnesium stearate
Purified water

Film coat

Opadry White

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of the container

The tablets are packed in PVC-Aluminium foil blister packs.

Pack size of 1 x 28 film-coated tablets (24 active and 4 placebo tablets).

6.6 Special precautions for disposal and other handling

This medicinal product may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT

Innovata Pharmaceuticals Ltd

100 Northern Parkway, Crownwood Office Park Block D, Ground Floor Ormonde

Johannesburg 2092

South Africa

8. MANUFACTURER

Oman Pharmaceutical Products Co., L.L.C

Plot No. 101, Raysut Industrial Estate, Salalah

Sultanate of Oman

9. REGISTRATION DETAILS

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Zimbabwe category for distribution: Prescription Preparations Tenth Schedule (P.P.10)

10. DATE OF REVISION OF TEXT

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