SCHEDULING STATUS

S4

1. NAME OF MEDICINE:

CONTREZ 3 mg/0.02 mg (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

CONTREZ (film-coated tablets)

24 hormonal tablets

Each film-coated tablet contains: 3 mg drospirenone and 0,02 mg ethinylestradiol.

Contains sugar: lactose monohydrate: 43.303 mg

4 inactive tablets (placebo)

The tablet does not contain active substances

Contains sugar: lactose monohydrate: 60.000 mg

For the full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM:

Film-coated tablets

CONTREZ 3 mg/0.02 mg (Active tablets)

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

Placebo (inactive tablets)

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

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

- Oral contraceptive.
- 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.

CONTREZ has not been evaluated for treatment of premenstrual syndrome (PMS).

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.

How to start CONTREZ:

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

The first tablet must be taken on day 1 of the woman'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.

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

Start with **CONTREZ** preferably on the day after the last active tablet 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 the event a vaginal ring or transdermal patch has been used, start using **CONTREZ** preferably on the day of removal, but at the latest when the next application would have been due.

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

The patient 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 a barrier method for the first 7 days of tablet-taking.

d) *Following first-trimester abortion:*

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

e) *Following delivery or second-trimester abortion:*

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 **CONTREZ** use or the woman must wait for her first menstrual period.

Management of missed tablets:

Placebo tablets from the last (4^{th}) 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 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 four 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:

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 cannot be excluded. The more tablets that are missed and the closer they are to the inactive tablet phase, the higher the risk of a pregnancy.

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.

Day 15 to 24:

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 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 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 tablets-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 4 days, including the days she missed tablets, and subsequently continue with the next pack, starting in the silver section with the tablets 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.

Advice in case of gastrointestinal disturbances:

In case of gastrointestinal disturbances, absorption may not be complete and additional contraceptive measure 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 **CONTREZ** 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 **CONTREZ** is then resumed after the inactive tablet phase.

Special populations:

Elderly

CONTREZ is not indicated after menopause.

Patients with hepatic impairment

CONTREZ is contraindicated in women with severe hepatic diseases. See also sections 4.3 and 5.2.

Patients with renal impairment

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

Paediatric population

CONTREZ is only indicated after menarche.

Method of administration

For oral use.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the

excipients listed in section 6.1.

Combined oral contraceptives such as **CONTREZ** 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 treatment with **CONTREZ**, 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, 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, TIA)
    - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant)
    - History of migraine with focal neurological symptoms

- The presence of a severe or multiple risk factor(s) for arterial thromboembolism (see section 4.4) such as:
    - diabetes mellitus with vascular symptoms
    - severe hypertension
    - severe dyslipoproteinaemia
- 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.
- Known or suspected pregnancy.
- **CONTREZ** is contraindicated for concomitant use with the medicine containing ombitasvir/ paritaprevir/ ritonavir and dasabuvir, (see sections 4.4 and 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 **CONTREZ** 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 healthcare provider to determine whether the use of **CONTREZ** should be discontinued.

In case of suspected or confirmed VTE or ATE, **CONTREZ** 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

The risk of VTE is highest during the first year of use. This increased risk is present after initially starting **CONTREZ** or restarting (following a 4 week or greater pill free interval) the same or a different combined oral contraceptive. This increased risk is mainly present during the first 3 months.

The overall risk for venous thromboembolism (VTE) in patients of low oestrogen dose combined oral contraceptives is two to threefold higher than for non-patients of combined oral contraceptives who are not pregnant.

Risk factors for VTE and ATE

The risk for venous and arterial thromboembolic complications in **CONTREZ** patients may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see table).

CONTREZ is contraindicated if a woman has multiple risk factors that put her at high risk of venous and 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 of VTE/ ATE should be considered. If the balance of benefits and risks is negative a combined hormonal contraceptive (CHC) should not be prescribed (see section 4.3).

Risk factors for VTE and ATE include:

- Obesity (body mass index over 30 kg/m^2)
    - Risk increases substantially as BMI rises. It is 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. 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 weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy.

    - Antithrombotic treatment should be considered if **CONTREZ** has not been discontinued in advance.
    - Note: temporary immobilisation including air travel > 4 hours can also be a risk factor for VTE, particularly in women with other risk factors

- Family history
    - 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 medical practitioner for advice before deciding about any **CONTREZ** 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
    - Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus.
- Increasing age
    - Particularly above 35 years
- Hypertension
- Smoking
    - Women should be advised not to smoke if they wish to use **CONTREZ**. Women over 35 who continue to smoke should be strongly advised to use a different method of contraception
- Migraine

- An increase in frequency or severity of migraine during **CONTREZ** use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation

The increased risk of thromboembolism in pregnancy, and particularly the 6-week period of the puerperium, must be considered (for information 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 **CONTREZ**.

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.

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 **CONTREZ**.

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:

The most important risk factor for cervical cancer is persistent human papilloma virus infection. Long-term use of combined oral contraceptives (COCs) may further contribute to an increased risk of cervical cancer.

There is a slightly increased relative risk (RR = 1,24) of having breast cancer diagnosed in women who are currently using **CONTREZ**. The excess risk gradually disappears during the course of the 10 years after cessation of **CONTREZ** use.

Benign liver tumours and, even more rarely, malignant liver tumours have been reported in patients of **CONTREZ**. 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 **CONTREZ**.

Other conditions

Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs such as **CONTREZ.**

Small increases in blood pressure have been reported in many women taking COCs and clinically relevant increases may occur. If a sustained clinically significant hypertension develops during the use of **CONTREZ,** then it is prudent for the medical practitioner to withdraw **CONTREZ** and treat the hypertension.

The occurrence or deterioration of the following conditions have been reported with COCs use 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.

In women with hereditary angioedema, exogenous oestrogens included in **CONTREZ** may induce or exacerbate symptoms of angioedema.

Acute or chronic disturbances of liver function may necessitate the discontinuation of **CONTREZ**. Recurrence of cholestatic jaundice which first occurred during pregnancy or previous use of sex steroids necessitates the discontinuation of **CONTREZ**.

CONTREZ may influence peripheral insulin resistance and glucose tolerance. Hence diabetic women should be carefully observed while taking **CONTREZ**. Crohn’s disease and ulcerative colitis have been associated with combined oral contraceptives such as **CONTREZ**.

Chloasma may 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 **CONTREZ**.

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 medical practitioner in case of mood changes and depressive symptoms, including shortly after initiating treatment.

Worsening of epilepsy, of Crohn's disease and of ulcerative colitis has been reported during COCs use.

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 medicines such as **CONTREZ** (see sections 4.3 and 4.5).

Medical examination/consultation:

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of **CONTREZ** use, guided by "**section 4.3**" and "**section 4.4"**, and should be repeated periodically. Periodic medical assessment is also of importance because contraindications (e.g. a transient ischaemic heart attack, etc) or risk factors (e.g. family history of venous or arterial thrombosis) may appear for the first time during the use of **CONTREZ**.

The frequency and nature of these assessments should be based on established practice guidelines and be adapted to the individual woman, but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests.

Women should be advised that **CONTREZ** does not protect against HIV infections (AIDS) and other sexually transmitted diseases (STDs). Women should be advised that additional barrier contraceptive measures are needed to prevent transmissions of STDs and HIV infection.

Reduced efficacy:

The efficacy of **CONTREZ** may be reduced in the event of e.g. missed active tablets, gastro-intestinal disturbances during active tablet taking (see "**section 4.2**") or concomitant medication (see "**section 4.5**").

Reduced cycle control:

Irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. 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. This may include curettage.

In some women withdrawal bleeding may not occur during the inactive tablet phase. If **CONTREZ** has been taken according to the directions described under "**section 4.2**", it is unlikely that the woman is pregnant. However, if **CONTREZ** 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 **CONTREZ** is continued.

Excipients

CONTREZ tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose -galactose malabsorption should not take CONTREZ.

4.5 Interaction with other medicines and other forms of interaction

Interactions between **CONTREZ** and other medicines may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature.

Hepatic metabolism:

Interactions can occur with medicines that induce microsomal enzymes, which can result in increased clearance of sex hormones (e.g. phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St John's Wort). HIV protease (e.g. ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine), and combinations of them, have been reported to potentially affect hepatic metabolism.

Enzyme inhibitors

Concomitant administration of strong CYP3A4 inhibitors can increase plasma concentrations of the oestrogen or the progestin or both. (e.g. ketoconazole, etoricoxib)

Other medicines

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

Based on in vivo interaction studies in female patients 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 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.

Interference with enterohepatic circulation:

Enterohepatic circulation of oestrogens may decrease when certain antibiotic medicines are given, which may reduce ethinylestradiol concentrations (e.g. penicillins, tetracyclines).

Women on treatment with any of these medicines should temporarily use a barrier method in addition to **CONTREZ** or choose another method of contraception. With microsomal enzyme-inducing medicines, the barrier method should be used during the time of concomitant medicine administration and for 28 days after their discontinuation. Women on treatment with antibiotics (except rifampicin and griseofulvin) should use the barrier method until 7 days after discontinuation. If the period during which the barrier method is used runs beyond the end of the active tablets in the **CONTREZ** pack, the inactive tablets should be omitted and the next pack of **CONTREZ** should be started with the active tablets (i.e. without the usual inactive tablet interval).

Other 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, **CONTREZ**-patients must switch to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy with this combination drug regimen. **CONTREZ** can be restarted 2 weeks following completion of treatment with this combination drug 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 **CONTREZ** 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.

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

Women of Childbearing Potential

CONTREZ is indicated for use by women of childbearing potential.

Refer to sections 4.1, 4.2, 4.3 and 4.4

Pregnancy

CONTREZ is not indicated during pregnancy. If pregnancy occurs during treatment with **CONTREZ**, further intake should be stopped.

Breastfeeding

The use of **CONTREZ** is not recommended during breastfeeding. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk.

Fertility

CONTREZ is a contraceptive. It is indicated for the prevention of pregnancy.

4.7 Effects on the ability to drive and use machines

CONTREZ can cause dizziness (see section 4.8) which may affect the ability to execute sound coordination and therefore influence the ability to drive and use machinery.

4.8 Undesirable effects

System Organ Class	Frequent	Less frequent	Frequency unknown
Infections and infestations		Candidiasis	
Blood and lymphatic system disorders		Anaemia, thrombocythemia	
Immune system disorders		Allergic reaction	Hypersensitivity
Endocrine disorders		Endocrine disorder	
Metabolism and nutrition disorders		Increased appetite, anorexia, hyperkalaemia, hyponatremia,	

Psychiatric disorders	Emotional lability	Depression, nervousness, somnolence, anorgasmia, insomnia	
Nervous system disorders	Headache	Dizziness, paraesthesia, vertigo, tremor	
Eye disorders		Conjunctivitis, dry eye, eye disorder	
Ear and labyrinth		Hypacusia	

disorders			
Cardiac disorders		Tachycardia	
Vascular disorders		Migraine, varicose vein, hypertension, hypotension, phlebitis, vascular disorder, epistaxis, syncope, venous thromboembolism (VTE), arterial thromboembolism (ATE),	
Respiratory,		Asthma	

thoracic and mediastinal disorders			
Gastrointestinal disorders	Nausea	Abdominal pain, vomiting, dyspepsia, flatulence, gastritis, diarrhoea, 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,	Erythema multiforme

		skin striae, contact dermatitis, photosensitive dermatitis, skin nodule	
Musculoskeletal and connective tissue disorders		Back pain, pain in extremity, muscle cramps	
Reproductive system and breast disorders	Breast pain, Metrorrhagia, amenorrhea , leukorrhoea, vaginal moniliasis, Intermenstrual	Vaginal candidiasis pelvic pain, breast enlargement, fibrocystic breast, uterine / vaginal bleeding,	

	bleeding	genital discharge, hot flushes, vaginitis, menstrual disorder, dysmenorrhea, hypomenorrhea, menorrhagia, vaginal dryness, papanicolaou smear suspicious, libido decreased, dyspareunia, vulvovaginitis, postcoital bleeding,	

		withdrawal bleeding, breast cyst, breast hyperplasia, breast neoplasm, cervical polyp, endometrial atrophy, ovarian cyst, uterine enlargement,	
General disorders and administration site conditions		Asthenia, sweating increased, oedema (generalized oedema,	

		peripheral oedema, face oedema), malaise,	
Investigations		weight increase, weight decrease	

The following serious side effects have been reported in women using COCs, which are discussed under section 4.4 Special warning and precautions for use:

- Venous thromboembolic disorders.

- Arterial thromboembolic disorders.

- Hypertension.

- Liver tumours.

- Occurrence or deterioration of conditions for which association with **CONTREZ** 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 **CONTREZ** use until markers of liver function return to normal.

- In women with hereditary angioedema exogenous oestrogens may induce or exacerbate symptoms of angioedema

The frequency of diagnosis of breast cancer is very slightly increased among **CONTREZ** patients. 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 **CONTREZ** 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 benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form",** found online under SAHPRA's publications: hppts://www.sahpra.or.za/Publications/Index/8

4.9 Overdose

On the basis of general experience with combined oral contraceptives, symptoms that may occur in case of taking an overdose of active tablets are nausea~~,~~, vomiting~~,~~, and, in young girls, slight vaginal bleeding. Treatment is symptomatic and supportive.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Category and class: A 21.8.2 Progesterones with oestrogens

Pharmacotherapeutic group (ATC):

Progestogens and oestrogens, fixed combinations ATC Code: G03AA12

The contraceptive effect of combined oral contraceptives 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.

CONTREZ 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 oestrogenic, glucocorticoid and antiglucocorticoid activity. This gives drospirenone a pharmacological profile closely resembling the natural hormone progesterone

5.2 Pharmacokinetic properties

- *Drospirenone*

Absorption

Orally administered drospirenone is rapidly and almost completely absorbed. Maximum concentrations of the active substance in serum of about 38 ng/mL are reached at about 1- to 2 hours after single ingestion. Bioavailability is between 76

and 85 %. The intake of food had no influence on the extent of absorption of drospirenone

Distribution

After oral administration, serum drospirenone levels decrease with a terminal half-life of 1,6 ± 0,7 hours and 27,0 ± 7,5 hours, respectively. 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 concentrations of the active substance are present as free steroid. The mean apparent volume of distribution of drospirenone is 3,7 ± 1,2 L/kg.

Biotransformation

Drospirenone is metabolised by cytochrome P450 3A4 and has demonstrated a capacity to inhibit this enzyme and cytochrome P450 1A1, cytochrome P450 2C9 and

cytochrome P450 2C19 in vitro. The major metabolites in plasma are the acid form of drospirenone, generated by opening of the lactone ring, and the 4,5-dihydro-drospirenone-3-sulfate, formed by reduction and subsequent sulfatation. Drospirenone is also subject to oxidative metabolism catalysed by 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 hours.

Steady-State Conditions

During a treatment cycle, maximum steady-state concentrations of drospirenone in serum of about 60 ng/mL are reached day 7 and day 14 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. Further accumulation of drospirenone levels beyond treatment

cycles was observed between cycles 1 and 6 but thereafter, no further accumulation was observed.

Special populations:

Effect of renal impairment:

Steady-state serum drospirenone levels in women with mild renal impairment (creatine clearance CLcr, 50 to 80 mL/min) were comparable to those of women with normal renal function (CLcr, > 80 mL/min). The serum drospirenone levels were on average 37 % higher in women with moderate renal impairment (CLcr, 30 to 50 mL/min) compared to those in women with normal renal function.

Drospirenone treatment did not show any clinically significant effect on serum potassium concentration.

Effect of hepatic impairment:

In women with moderate hepatic function (Child Pugh B), mean serum drospirenone concentration-time profiles were comparable to those of women with normal hepatic function.

- *Ethinylestradiol*

Absorption

Orally administered ethinylestradiol is absorbed rapidly and completely. Peak serum concentrations of about 88 to 100 pg/mL are reached within 1 to 2 hours after single oral administration. Absolute bioavailability because 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 patients 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 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 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

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 1,4 to 2,1.

6. Pharmaceutical particulars

6.1 List of excipients

Croscarmellose sodium, hypromellose, iron oxide red, lactose monohydrate magnesium stearate, macrogol, maize starch, opadry pink, opadry white, povidone, pregelatinised starch, purified water, titanium dioxide.

6.2 Incompatibilities

None

6.3 Shelf life

30 months

6.4 Special precautions for storage

Store at or below 30ºC.

6.5 Nature and contents of container

Drospirenone / Ethinylestradiol film-coated tablets are packed in blisters of PVC/ aluminum foil. The blisters are packaged in a carton box along with package insert

6.6 Special precautions for disposal and other handling

No special requirements

7. Holder of certificate of registration

Innovata Pharmaceuticals

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

2091

South Africa

8. Registration numbers

A 50/21.8.2/0517

9. Date of first authorization/Renewal of the authorization

25/10/2022

10. Date of revision of the text

02/09/2025