PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

OCAZ 3,0/0,03 Film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each yellow active film-coated tablet contains

Drospirenone 3 mg

Ethinyl estradiol 0,03 mg

Each white to off white inactive film coated tablet of OCAZ contains no active substance.

Excipients with known effect

Each active film-coated tablet contains sugar (lactose monohydrate 66,17 mg).

Each inactive film-coated tablet contains sugar (lactose monohydrate 69,20 mg).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated active tablets

Yellow coloured round biconvex film coated tablets, debossed with “DR2” on one side and plain on the other side.

Film-coated inactive tablets

White to off white round, biconvex film coated tablets debossed with “K33” on one side and “LU” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception.

4.2 Posology and method of administration

How to take OCAZ:

Combined oral contraceptives (COC), 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 OCAZ 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., "MO" 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 OCAZ during the latter part of the week, the very first cycle may be slightly shortened.

How to start OCAZ:

***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 OCAZ 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 OCAZ 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 to off white film-coated tablets can be disregarded. However, they should be discarded to avoid unintentionally prolonging the hormone-free tablet phase. The following advice only refers to missed hormone-containing light 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 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 to off 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 OCAZ 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 OCAZ is then resumed after the inactive tablet phase.

Additional information on special populations:

Children and adolescents:

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

Elderly patients:

Not applicable. OCAZ is not indicated after menopause.

***Patients with hepatic impairment*:**

OCAZ is contraindicated in women with severe hepatic diseases. See also section 4.3 and section 5.2.

Patients with renal impairment:

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

Method of administration:

For oral use only.

4.3. Contraindications

OCAZ 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 OCAZ use, the product should be stopped immediately.

- Hypersensitivity to the active substances [Drospireone (3 mg) and ethinyl estradiol (0,03 mg)] 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 (including Factor V Leiden), 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 (current stroke, history of stroke).
- Presence or history of prodroma of a thrombosis (e.g., transient ischaemic attack, angina pectoris), major surgery with prolonged immobilisation.
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contra-indication (see section 4.4).
- History of migraine with focal neurological symptoms.

- Diabetes mellitus with vascular involvement.
- 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 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.
- Depression not well-controlled with treatment.
- A history of depression with the use of hormonal contraception.

OCAZ is contraindicated for concomitant use with the medicines containing ombitasvir/paritaprevir/ritonavir and dasabuvir.

4.4. Special warnings and precautions for use

If any of the conditions/risk factors mentioned below are present, the benefits of OCAZ should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her medical practitioner. The medical practitioner should then decide on whether OCAZ use 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:

An association between the use of combined oral contraceptives and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, deep venous thrombosis, pulmonary embolism and of cerebrovascular accidents has been reported.

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

Overall, the risk for venous thromboembolism (VTE) in users of low combined oral contraceptives is two to threefold higher than for non-users of combined oral contraceptives who are not pregnant.
Venous thromboembolism (VTE) may be life-threatening or may have a fatal outcome (in 1 to 2 % of the cases).

The occurrence of thrombosis has been reported in other blood vessels, e.g., hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in combined oral contraceptive including OCAZ users. There is no consensus as to whether the occurrence of these events is associated with the use of combined oral contraceptives such as drospirenone 3 mg and ethinylestradiol 0,03 mg as in OCAZ:

Symptoms of deep venous thrombosis (DVT) can include unilateral swelling of the leg 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 bring up blood; sharp chest pain which may increase with deep breathing; sense of anxiety; 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).

An arterial thromboembolic event can include cerebrovascular accident, vascular occlusion or myocardial infarction (MI). 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 confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, loss of balance or coordination; sudden, severe or prolonged headache with no known cause; loss of consciousness or fainting with or without seizure. Other signs of vascular occlusion can include sudden pain, swelling and slight blue discoloration of an extremity; acute abdomen. 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 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; fullness, indigestion or choking feeling; sweating, nausea, vomiting or dizziness; extreme weakness, anxiety, or shortness of breath; rapid or irregular heartbeats.

Arterial thromboembolic events may be life-threatening or may have a fatal outcome. The risk of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident increases with:

- Age.

- Smoking (with heavier smoking and increasing age the risk increases further, especially in women over 35 years of age).
- A positive family history (i.e., venous, or arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is known or suspected, the woman should be referred to a specialist for advice before deciding about any combined oral contraceptive use.
- Obesity (body mass index over 30 kg/m^2).
- Dyslipoproteinaemia.
- Hypertension.
- Migraine.
- Valvular heart disease.
- Atrial fibrillation.
- Prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations, it is advisable to discontinue combined oral contraceptive use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation.
- Hyperhomocysteinaemia

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in venous thromboembolism.

The increased risk of thromboembolism in the puerperium must be considered (see section 4.6).

Other medical conditions which have been reported to be associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis), cancer and sickle cell disease.

An increase in frequency or severity of migraine during combined oral contraceptive use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the combined oral contraceptive.

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinaemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

Tumours:

The most important risk factor for cervical cancer is persistent human papilloma virus infection. Long-term use of combined oral contraceptives may further contribute to this increased risk but there continues to be controversy about the extent to which this reported finding is attributable to confounding effects, e.g., cervical screening and sexual behaviour including use of barrier contraceptives.

A slightly increased relative risk (RR = 1,24) of having breast cancer diagnosed has been reported in women who are currently using combined oral contraceptives. The excess risk has been reported to gradually disappear during the 10 years after cessation of combined oral contraceptive use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent combined oral contraceptive users is small in relation to the overall risk of breast cancer.

Benign liver tumours, and malignant liver tumours have been reported in users of combined oral contraceptives. These tumours have been reported to lead 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 combined oral contraceptives.

Malignancies may be life-threatening or may have a fatal outcome.

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

Other conditions:

Potassium excretion capacity may be limited in patients with renal insufficiency.
Drospirenone intake did not reportedly show an effect on the serum potassium concentration in patients with mild or moderate renal impairment. A theoretical risk for hyperkalaemia can be assumed only for patients with renal impairment whose pre-treatment serum potassium is in the upper reference range, and who are additionally using potassium-sparing medicines.
Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using drospirenone 3 mg and ethinylestradiol 0,03 mg, as in OCAZ.

Small increases in blood pressure have been reported in many women taking combined oral contraceptives containing ethinyl estradiol, clinically relevant increases may occur. If a sustained clinically significant hypertension develops during the use of OCAZ then it is prudent for the medical practitioner to withdraw it.

The following conditions have been reported to occur but the evidence of an association with OCAZ: 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.
In women with hereditary angioedema exogenous oestrogens may induce or exacerbate symptoms of angioedema.

Acute or chronic disturbances of liver function may necessitate the discontinuation of OCAZ: until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of OCAZ

Although drospirenone 3 mg and ethinyl estradiol 0,03 mg, as in OCAZ: may have an effect on peripheral insulin resistance and glucose tolerance, there is no reported evidence for a need to alter the therapeutic regimen in diabetics using OCAZ due to its low ethinyl estradiol content of 0,03 mg. However, diabetic women should be carefully observed while taking OCAZ.

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

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use. Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their medical practitioner in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

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 OCAZ.

Respiratory: Asthma may deteriorate in women using OCAZ drospirenone 3 mg and ethinyl estradiol 0,03 mg.

ALT elevations:

In 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) has been reported to occur

significantly more frequent in women using ethinyl estradiol-containing medicines such as combined hormonal contraceptives (CHCs).

Special precautions:

Medical examination/consultation:

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of combined oral contraceptive use, guided by the sections 4.3 and 4.4, and should be repeated periodically. Periodic medical assessment is also of importance because contraindications (e.g., a transient ischaemic attack, etc.) or risk factors (e.g., a family history of venous or arterial thrombosis) may appear for the first time during the use of a combined oral contraceptive such as drospirenone 3 mg and ethinyl estradiol 0,03 mg as in OCAZ. 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.

Women should be advised that OCAZ does not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Reduced efficacy:

The efficacy of combined oral contraceptives such as drospirenone 3 mg and ethinyl estradiol 0,03 mg may be reduced in the event of e.g., missed active tablets, gastrointestinal 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. 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 inactive tablet phase. If OCAZ has been taken according to the directions described under section 4.2, it is unlikely that the woman is pregnant. However, if OCAZ 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 OCAZ use is continued.

Excipients

OCAZ contains the sugar lactose monohydrate (active tablet contains 66, 17 mg and inactive tablet contains 69,20 mg). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interaction with other medicines and other forms of interaction

Effects of other medicines on OCAZ

Interactions between OCAZ and other medicines (enzyme inducers, some antibiotics) 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 medicinal 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 the COC. The barrier method must

be used during the whole time of the concomitant medicine therapy and for 28 days after its discontinuation. If the medicine therapy runs beyond the end of the tablets in the COC pack, the next COC 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 active substances, another reliable, non-hormonal, method of contraception is recommended.

The following interactions have been reported in the literature.

Medicines diminishing the efficacy of combined oral contraceptives such as drospirenone 3 mg and ethinylestradiol 0,03 mg (enzyme-inducers and antibiotics):

Enzyme induction (increase of 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, bosentan, rifampicin, efavirenz and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St John's Wort).

Also, HIV protease inhibitors (e.g., ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine), and combinations of them, have been reported to potentially affect hepatic metabolism.

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

In a reported multiple dose study with a drospirenone (3 mg/day) / ethinyl estradiol (0,02 mg/day) combination, co-administration of the strong CYP3A4 inhibitor ketoconazole for 10

days increased the $AUC_{(0-24h)}$ of drospirenone and ethinyl estradiol 2,7-fold and 1,4-fold respectively.

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

Antibiotics (interference with enterohepatic circulation):

Enterohepatic circulation of oestrogens may decrease when certain antibiotics are given, which may reduce ethinyl estradiol concentrations (e.g., penicillins, tetracyclines).

Women on treatment with any of these medicines should temporarily use a barrier method in addition to OCAZ 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 OCAZ pack, the white to off white inactive tablets should be omitted and the next OCAZ pack should be started with the yellow active tablet in the silver section (i.e., without the usual inactive tablet interval).

Substances interfering with the metabolism of combined oral contraceptives such as drospirenone 3 mg and ethinyl estradiol 0,03 mg, as in OCAZ (enzyme inhibitors):

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.

Effects of combined oral contraceptives such as OCAZ on other medicines:

OCAZ 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 reported in vitro inhibition studies and in vivo interaction studies in female volunteers using omeprazole, simvastatin and midazolam as marker substrates, an interaction of drospirenone at doses of 3 mg with the metabolism of other medicines is unlikely.

Clinical data suggest that ethinyl estradiol may inhibit the clearance of CYP1A2 substrates leading to a weak (e.g. theophylline) or moderate (e.g. tizanidine) increase in their plasma concentration.

Other interactions:

There is a theoretical potential for an increase in serum potassium in women taking drospirenone 3 mg and ethinyl estradiol 0,03 mg, as in OCAZ with other medicines that may increase serum potassium levels. Such medicines include angiotensin-II-receptor antagonists, potassium-sparing diuretics, and aldosterone antagonists. However, in studies evaluating the interaction of drospirenone (combined with estradiol) with an ACE inhibitor or indomethacin, no clinically or statistically significant differences in serum potassium concentrations were reported.

Concomitant use with the medicines containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations.

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

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

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. Anti-mineralocorticoid activity of drospirenone causes an increase in plasma renin activity and induces plasma aldosterone.

4.6. Fertility, pregnancy, and lactation

Pregnancy:

OCAZ is contraindicated during pregnancy. If pregnancy occurs during treatment with OCAZ, further intake must be stopped.

The increased risk of VTE during the postpartum period should be considered when re-starting OCAZ.

Breastfeeding: Ref 1, page 21, A

Lactation may be influenced by combined oral contraceptives as they may reduce the quantity and change the composition of breast milk. Therefore, the use of OCAZ is not 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. 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 reported. No effects on ability to drive and use machines have been reported in users of OCAZ tablets.

However OCAZ may cause migraine. Patients should be advised that they should determine how OCAZ affects them before they can engage in these activities.

4.8. Undesirable effects

The most serious adverse effects associated with the use of combined oral contraceptives are also listed under section 4.4.

The frequencies of side effects reported with OCAZ tablets are summarised in the table below. Within each frequency grouping, side effects are presented in order of decreasing seriousness.

System Organ Class (MedDRA)	Frequent	Less frequent
Immune system disorders		Hypersensitivity
Metabolism and nutrition disorders		Fluid retention
Psychiatric disorders	Depression/depressive mood, emotional lability, decrease and loss of libido	Increased libido
Nervous system disorders	Headache	
Eye disorders		Contact lens intolerance
Ear and labyrinth disorders		Hypoacusis
Respiratory disorders		Asthma
Vascular disorders	Migraine	Venous and arterial thromboembolic events (peripheral deep venous occlusion, thrombosis and embolism/pulmonary vascular occlusion, thrombosis, embolism and infarction/myocardial infarction /cerebral infarction and stroke not specified as haemorrhagic), hypertension, hypotension

System Organ Class (MedDRA)	Frequent	Less frequent
Gastrointestinal disorders	Nausea, abdominal pain	Vomiting, diarrhoea
Skin and subcutaneous tissue disorders		Rash, urticaria, erythema nodosum, erythema multiforme, acne, eczema, pruritus, alopecia
Reproductive system and breast disorders	Breast pain, unscheduled uterine bleeding, genital tract bleeding not further specified, breast tenderness, menstrual disorders, vaginal discharge, vulvovaginal candidiasis	Breast hypertrophy, vaginal infection, breast discharge
Investigations	Increased weight	Decreased weight

Description of selected adverse reactions:

Adverse reactions with low frequency or with delayed onset of symptoms which are considered related to the group of combined oral contraceptives, including OCAZ tablets, are listed below (see sections 4.3 and 4.4):

Tumours:

- The frequency of diagnosis of breast cancer is slightly increased among OC 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.
- Liver tumours (benign and malignant).

Other conditions:

- Women with hypertriglyceridaemia (increased risk of pancreatitis when using COCs).
- Hypertension.
- Occurrence or deterioration of conditions for which association with COC use is not conclusive: jaundice and/or pruritus related to cholestasis; gallstone formation;

porphyria; systemic lupus erythematosus; haemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

- In women with hereditary angioedema exogenous oestrogens may induce or exacerbate symptoms of angioedema.
- Liver function disturbances.
- Changes in glucose tolerance or effect on peripheral insulin resistance.
- Crohn's disease, ulcerative colitis.
- Chloasma.

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. Health care providers 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

4.9. Overdose

There has not been any reported clinical experience of overdose with OCAZ. There have been no reports of serious deleterious effects from overdose in preclinical studies. On this basis of general experience with combined oral contraceptives, symptoms that may occur in this case are nausea, vomiting and, in young girls, slight vaginal bleeding. Withdrawal bleeding may even occur in girls before their menarche if they accidentally take the medicine. There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 18.8 Ovulation controlling agents

Pharmacotherapeutic group (ATC): Progestogens and oestrogens, fixed combinations

ATC Code: G03AA 12

The contraceptive effect of drospirenone 3 mg and ethinyl estradiol 0,03 mg tablets 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. OCAZ is a combined oral contraceptive with ethinyl estradiol and the progestogen, drospirenone. In a therapeutic dosage, drospirenone also possesses antiandrogenic and mild anti-mineralocorticoid properties. It has no oestrogenic, glucocorticoid and anti-glucocorticoid activity.

There are indications from clinical studies that the mild anti-mineralocorticoid properties of drospirenone 3 mg and ethinyl estradiol 0,03 mg tablets result in a mild anti-mineralocorticoid effect.

With the use of the higher dosed combined oral contraceptives (50 µg ethinyl estradiol) 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

Drospirenone

Absorption*:*

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.

Distribution:

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 medicine concentrations are present as free steroid, 95 to 97 % are non-specifically bound to albumin. The ethinyl estradiol-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.

Biotransformation:

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 ethinyl estradiol, no direct interaction was reported.

Elimination:

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.

Steady-state conditions:

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

Special populations:

- ***Effect of renal impairment:***

Steady-state serum drospirenone levels in women with mild renal impairment (creatinine clearance CLcr, 50 to 80 mL/minute) were reported to be comparable to those of women with normal renal function (CLcr, > 80 mL/minute). The serum drospirenone levels were reported to be 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 reported to be well tolerated by all groups. It has been reported that 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 reported to be 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 reported to be about 1,8 times greater than for the volunteers with normal hepatic function.

An about 50 % decrease in apparent oral clearance (CL/f) was reported in volunteers with moderate hepatic impairment as compared to those with normal liver function. The reported 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.

Ethinyl estradiol

Absorption:

Orally administered ethinyl estradiol 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, ethinyl estradiol 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 has been reported to reduce the bioavailability of ethinyl estradiol in about 25 % of the investigated subjects while no change was reported in the others.

Distribution:

Ethinyl estradiol 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:

Ethinyl estradiol is subject to presystemic conjugation in both the small bowel mucosa and the liver. Ethinyl estradiol 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:

Ethinyl estradiol 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, ethinyl estradiol 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:

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Active film coated tablets

Tablet core:

Lactose monohydrate

Corn starch

Methylene chloride

Pregelatinised starch

Magnesium stearate

Tablet coating:

Opadry yellow 03F82726

Inactive film coated tablets

Tablet core:

Lactose monohydrate

Corn starch

Pregelatinised starch

Magnesium stearate

Tablet coating:

Opadry white 03B28796

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original packaging.

Do not use the tablets after the expiry date printed on the container.

6.5 Nature and contents of container

The medicine is packaged in a carton containing one clear PVC, printed aluminium foil blister strip.

6.6 Special precautions for disposal and other handling

Return all unused or expired medicines to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewerage systems (e.g., toilets).

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

Cnr. Searle & Pontac Streets

8001, Cape Town

South Africa

8. REGISTRATION NUMBER

47/18.8/0159

9. DATE OF FIRST AUTHORISATION

10 August 2022

10. DATE OF REVISION OF THE TEXT