Approved Professional Information for Medicines for Human Use:

LEYLA

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

LEYLA 0,02 mg/3 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The 28-day pack (every-day pack) contains:

- 24 Active film-coated tablets (pink) each containing
  - drospirenone 3 mg and
  - ethinyl estradiol 0,02 mg.
- 4 Inactive (placebo) film-coated tablets (white) each containing no active ingredients.

Contains sugar (lactose).

Each LEYLA active film-coated tablet (pink) contains 41,8 mg lactose as 44 mg lactose monohydrate.

Each LEYLA inactive film-coated tablet (white) contains 89,5 mg lactose as 89,5 mg anhydrous lactose.

Contains less than 1 mmol sodium per dose.

Each LEYLA active film-coated tablet (pink) contains 0,225 mg (0,0098 mmol) sodium, that is to say essentially 'sodium-free'.

Each LEYLA inactive film-coated tablet (white) is 'sodium-free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

The LEYLA active film-coated tablet is pink, round with a 5,7 mm diameter.

The LEYLA inactive tablet is white, round with a 5,7 mm diameter.

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. The efficacy of Drosperinone 3 mg/Ethinyl estradiol 0,02 mg tablets for PMDD was not assessed beyond 3 cycles.

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

4.2 Posology and method of administration

Posology

How to start LEYLA

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 (CHC) [i.e. combination oral contraceptive (COC), vaginal ring or transdermal patch]

The woman should start with LEYLA 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 inactive tablet interval of her previous COC. In case a vaginal ring or transdermal patch has been used the woman should start using LEYLA 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 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 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 LEYLA use or the woman has to wait for her first menstrual period.

Management of missed tablets

Missed white pills (from the last row of the blister) are inactive and thus can be disregarded to avoid unintentionally prolonging the inactive tablet phase. The following advice only pertains to missed active tablets (tablets 1 - 24 of your blister-strip):

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 4 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 – 7 (first row)

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 are missed and the closer they are to the inactive tablet phase, the higher the risk of a pregnancy.

Day 8 – 14 (second row)

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 (third or fourth row)

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 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, 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 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 inactive tablets from the last row for up to 4 days, including the days she missed tablets, and subsequently continue with the next pack, starting with the active tablets on the upper left of the pack.

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

Advice in case of gastro-intestinal disturbances

In case of severe gastro-intestinal disturbances (e.g., vomiting or diarrhoea), 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 reserve pack.

How to delay a period

To delay a period the woman should continue with another blister pack of LEYLA 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 LEYLA is then resumed after the inactive tablet phase.

Special populations

Elderly population

LEYLA is not indicated after menopause.

Renal impairment

LEYLA is contraindicated in patients with severe renal impairment or acute renal failure (see section 4.3)

Hepatic impairment

LEYLA is contraindicated in women with severe hepatic diseases as long as liver function values have not returned to normal (see section 4.3).

Paediatric population

LEYLA is only indicated after menarche.

Method of administration

For oral use only.

LEYLA, when taken correctly, has a failure rate of approximately 1 % per year. The failure rate may increase when pills are missed or taken incorrectly.

Tablets must be taken in the order directed on the package, at about the same time every day, and swallowed whole with some liquid if needed. The tablets can be taken with or without food. 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 the inactive tablets (white tablets in the last row) and may not be finished before the next pack is started.

4.3 Contraindications

Combined oral contraceptives (COCs) such as LEYLA 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 LEYLA, the product should be stopped immediately.

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Known hereditary or acquired predisposition for venous or arterial thromboembolism, such as APC-resistance, (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia, antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant)
- Presence or a history of venous or arterial thrombotic/thromboembolic events (e.g., deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, or of a cerebrovascular accident)

- Presence or history of prodromata of a thrombosis (e.g., transient ischaemic attack, angina pectoris)
- History of migraine with focal neurological symptoms
- Diabetes mellitus with vascular involvement
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis (see “section 4.4”)
- Severe hepatic disease as long as liver function values have not returned to normal
- Severe renal insufficiency or acute renal failure with creatinine 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 (see section 4.6)
- Major surgery with prolonged immobilisation
- Severe hypertension, severe dyslipoproteinaemia
- Depression not well-controlled with treatment
- A history of depression with the use of hormonal contraceptives.

LEYLA is contraindicated for concomitant use with the medicines containing ombitasvir/paritaprevir/ritonavir and dasabuvir (see sections 4.4 and section 4.5).

4.4 Special warnings and precautions for use

Warnings

If any of the conditions or risk factors mentioned below are present, the suitability of LEYLA should be discussed with the woman.

In the event of aggravation, or first appearance of any of these conditions or risk factors, the woman should be advised to contact her doctor to determine whether the use of LEYLA should be discontinued.

In case of suspected or confirmed venous thromboembolism (VTE) or arterial thromboembolism (ATE), combined hormonal contraceptive (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 drospirenone/ethinyl estradiol, as in LEYLA tablets and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism has been reported.

Medicines that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. Other medicines products such as LEYLA tablets may have up to twice this level of risk. The decision to use any medicines 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 LEYLA, how her current risk factors influence this risk, and that her VTE risk is highest in the first year of use. There is also some reported evidence that the risk is increased when the same CHC is re-started or a different CHC is started after a break in use of 4 weeks or more. This increased risk is reported to be mainly present during the first 3 months.

Overall, the risk for venous thromboembolism (VTE) in users of low estrogen dose combined oral contraceptives is reported to be two to threefold higher than for non-users of combined oral contraceptives who are not pregnant.

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

Venous thromboembolism, manifesting as deep venous thrombosis and/or pulmonary embolism, may occur. The occurrence of thrombosis has been reported in other blood vessels, e.g., hepatic, mesenteric, renal, cerebral, or retinal veins and arteries, in LEYLA users.

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

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 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/m²)
- dyslipoproteinaemia
- hypertension
- migraine
- valvular heart disease

- atrial fibrillation
- prolonged immobilisation, major surgery, any surgery to the legs, or major trauma, temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors. In these situations, it is advisable to discontinue 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.

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

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

An increase in frequency or severity of migraine during LEYLA tablets use (which may be prodromal of a cerebrovascular event) may be a reason for its immediate discontinuation.

Biochemical factors that may be indicative of a 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 (HPV) infection. Long-term use of LEYLA may further contribute to an increased risk of cervical cancer.

A slightly increased relative risk (RR = 1,24) of having breast cancer diagnosed in women who are currently using drospirenone/ethinyl estradiol, as contained in LEYLA has been reported. The excess risk is reported to gradually disappear during the 10 years after cessation of drospirenone/ethinyl estradiol as contained in LEYLA use.

Benign liver tumours and, even more rarely, malignant liver tumours have been reported in users of drospirenone/ethinyl estradiol, as contained in LEYLA. In isolated cases, these tumours have been reported to lead to life-threatening intraabdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intraabdominal haemorrhage occur in women taking LEYLA.

With the use of the higher-dosed combined oral contraceptives (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

Renal impairment

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

Hypertriglyceridemia

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using combined oral contraceptives (COCs) such as LEYLA.

Hypertension

Small increases in blood pressure have been reported in many women taking drospirenone/ethinyl estradiol, as contained in LEYLA, and clinically relevant increases may occur.

If a sustained clinically significant hypertension develops during the use of LEYLA then it is prudent for the medical practitioner to withdraw it and treat the hypertension.

Conditions occurring and deteriorating with both pregnancy and COC use

The occurrence or deterioration of the following conditions have been reported with both pregnancy and drospirenone/ethinyl estradiol as contained in LEYLA 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.

Angioedema

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

Liver function disturbances

Acute or chronic disturbances of liver function may necessitate the discontinuation of LEYLA use until markers of liver function return to normal. Recurrence of cholestatic jaundice and/or

cholestasis-related pruritus which previously occurred during pregnancy or during previous use of sex steroids necessitates the discontinuation of LEYLA.

Diabetes

LEYLA may have an effect on peripheral insulin resistance and glucose tolerance. Hence diabetic women should be carefully observed while taking LEYLA, particularly in the early stage of LEYLA use.

Epilepsy, Crohn's disease and ulcerative colitis

Worsening of epilepsy, of Crohn's disease and of ulcerative colitis has been reported with combined oral contraceptives, such as LEYLA.

Depression

Worsening of endogenous depression has been reported during COC use, such as LEYLA.

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 practitioners in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Chloasma

Chloasma may occur, especially in women with a history of chloasma gravidarum (see section 4.8). Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking LEYLA.

Concomitant use with antibiotics

Oral contraceptive failure may occur with concomitant antibiotic therapy. For maximal protection, women on treatment with antibiotics should use additional non-hormonal contraception (barrier method) for the duration of antibiotic therapy and for seven days after discontinuation (see section 4.5).

Those on long-term antibiotic therapy (except rifampicin and griseofulvin) need only take extra precautions for the first two weeks of antibiotic therapy (see section 4.5). In women on long-term antibiotic treatment containing hepatic enzyme-inducing active substances, such as rifampicin and griseofulvin, another reliable, non-hormonal, method of contraception is recommended during the time of concomitant medicine administration and for 28 days after their discontinuation (see section 4.5).

Spotting and breakthrough bleeding are possible signs of diminished contraceptive effectiveness**.**

ALT elevations

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) have been reported significantly more frequent in women using ethinyl estradiol-containing medicines such as combined hormonal contraceptives (CHCs) (see sections 4.3 and 4.5).

Medical examination/consultation

A complete medical history (including family history) and physical examination should be taken, and pregnancy must be ruled out prior to the initiation or reinstitution of LEYLA use,

guided by the “Contraindications” (see section 4.3) and “Warnings” (see section 4.4), and should be repeated periodically.

Periodic medical assessment is also of importance because contra-indications (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 LEYLA. 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, abdominal and pelvic organs, including cervical cytology and relevant laboratory tests.

The woman should also be instructed to carefully read the patient information leaflet and to adhere to the advice given.

Women should be advised that LEYLA 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 transmission of STDs and HIV infection.

Reduced efficacy

The efficacy of LEYLA 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. 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 LEYLA has been taken according to the directions described under section 4.2, it is unlikely that the woman is pregnant. However, if LEYLA 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 LEYLA use is continued.

Excipient lactose

LEYLA contains lactose.
Each pink tablet of this medicine contains 41,8 mg lactose and each white tablet contains 89,5 mg lactose (see section 2).

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

Sodium

Contains less than 1 mmol sodium per dose.
Each LEYLA active film-coated tablet (pink) contains 0,225 mg (0,0098 mmol) sodium, that is to say essentially 'sodium-free'.

Each LEYLA inactive film-coated tablet (white) is 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Interactions between LEYLA and other medicines that induce microsomal enzymes have been reported and which can result in increased clearance of sex hormones which may lead to breakthrough bleeding and/or contraceptive failure.

The following interactions have been reported in the literature.

Note: The professional information of concomitant medicines should be consulted to identify potential interactions.

Effects of other medicines on LEYLA

Management

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

Short-term treatment

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

Please refer to section "*Additional contraceptive measures*" below.

Hepatic metabolism

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

Interactions can occur with medicines that induce microsomal enzymes, which can result in increased clearance of sex hormones e.g., barbiturates, bosentan, carbamazepine, phenytoin, primidone, rifampicin and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and products containing St. John's Wort (*Hypericum perforatum*).

Please refer to section "*Additional contraceptive measures*" below.

Antibiotics and interference with enterohepatic circulation

Some clinical reports suggest that enterohepatic circulation of estrogens may decrease when certain antibiotics are given, which may reduce ethinyl estradiol concentrations (e.g., penicillins, tetracyclines) (see section 4.4).

Please refer to section "*Additional contraceptive measures*" below.

Medicines with variable effects on the clearance of COCs

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

Please refer to section "*Additional contraceptive measures*" below.

Additional contraceptive measures

Women on treatment with any of these medicines increasing the clearance of COCs (e.g., microsomal enzyme inducers) or interfering with enterohepatic circulation (e.g., certain antibiotics) should temporarily use a barrier method in addition to LEYLA 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 (see section 4.4).

If the period during which the barrier method is used runs beyond the end of the active tablets in the LEYLA pack, the inactive tablets should be omitted and the next pack of LEYLA should be started with the active tablets on the upper left of the pack (i.e., without the usual inactive tablet interval).

Medicines decreasing the clearance of COCs (enzyme inhibitors)

Concomitant administration of strong CYP3A4 inhibitors can increase plasma concentrations of the estrogen 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 shown 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.

Clearance of drosperinone

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 LEYLA on other medicines

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

The reported clinical data suggests 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.

Pharmacodynamic interactions

Medicines containing ombitasvir/paritaprevir/ritonavir and dasabuvir

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, LEYLA 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. LEYLA can be restarted 2 weeks following completion of treatment with this combination regimen.

Other

There is a potential for an increase in serum potassium in women taking LEYLA 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. See also section 4.4.

No formal interaction studies were reported with tuberculosis or HIV treatments.

Other forms of 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. Drospirenone causes an increase in plasma renin activity and plasma aldosterone induced by its mild antimineralocorticoid activity.

4.6 Fertility, pregnancy and lactation

Pregnancy

LEYLA is contraindicated during pregnancy (see section 4.3).

If pregnancy occurs during treatment with LEYLA, further intake should be stopped.

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

Breastfeeding

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

Fertility

LEYLA is indicated for the prevention of pregnancy.

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 observed in users of COCs such as LEYLA.

However, patients should be advised that they may experience undesirable effects such as somnolence, dizziness, or vertigo during treatment (see section 4.8). Therefore, caution should be recommended when driving a vehicle or operating machinery.

4.8 Undesirable effects

The frequencies of adverse reactions (ARs) reported with drospirenone/ethinyl estradiol are summarised in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
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 Hyponatraemia Body weight changes Fluid retention	

		Hypertriglyceridaemia	
Psychiatric disorders	Depressive mood Emotional lability	Changes in libido Nervousness Somnolence Anorgasmia Insomnia	Altered mood
Nervous system disorders	Headache Migraine	Dizziness Paraesthesia Vertigo Tremor	
Eye disorders		Conjunctivitis Dry eye Eye disorder	Contact lens intolerance
Ear and labyrinth disorders		Hypoacusis	
Cardiac disorders		Tachycardia	
Vascular disorders		Hypertension Hypotension	

		Thromboembolism Varicose vein Phlebitis Vascular disorder Epistaxis Syncope Venous thrombo-embolism (VTE) Arterial thrombo-embolism (ATE) Cerebrovascular accidents	
Respiratory, thoracic and mediastinal disorders		Asthma	
Gastrointestinal disorders	Nausea	Vomiting Dyspepsia Flatulence Gastritis Abdominal pain Diarrhoea	

		Abdomen enlarged Gastrointestinal disorder Gastrointestinal fullness Hiatus hernia Oral candidiasis Constipation Dry mouth	
Hepatobiliary disorders		Biliary pain Cholecystitis Liver tumours (benign and malignant), Liver function disturbances	
Skin and subcutaneous tissue disorders		Acne Eczema Pruritus Rash Chloasma	Urticaria Erythema multiforme

		Alopecia Dermatitis acneiform Dry skin Erythema nodosum Hypertrichosis Skin disorder 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* Leukorrhoea** Vaginal moniliasis	Vaginitis Breast discharge Vaginal candidiasis Pelvic pain	

	Menstrual disorder (Metrorrhagia*** Amenorrhoea) Intermenstrual bleeding***	Breast enlargement Fibrocystic breast Uterine/Vaginal bleeding* Genital discharge Hot flushes Dysmenorrhea Hypomenorrhea Vaginal dryness Papanicolaou smear suspicious Libido decreased	
General disorders and administration site conditions		Asthenia Sweating increased Oedema (Generalized oedema, Peripheral oedema, Face oedema) Malaise	

* including breast tenderness

** including vaginal discharge

*** bleeding irregularities usually subside during continued treatment

Description of selected adverse reactions

An increased risk of arterial and venous thrombotic and thrombo-embolic events, including myocardial infarction, stroke, transient ischemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs, which are discussed in more detail in section 4.4.

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

- Venous thromboembolic disorders
- Arterial thromboembolic disorders
- Hypertension
- Liver tumours
- Occurrence or deterioration of conditions for which association with COC use is not conclusive: Crohn’s disease, ulcerative colitis, epilepsy, uterine myoma, porphyria, systemic lupus erythematosus, herpes gestationis, Sydenham's chorea, haemolytic uremic syndrome, cholestatic jaundice
- Chloasma

- Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal
- In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

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

Interactions

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

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 should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.8.2 Progesterones with estrogens

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

ATC Code: G03AA12

Mechanism of action

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.

Drospirenone exerts antiandrogenic activity.

Drospirenone is devoid of androgenic, oestrogenic, glucocorticoid and antiglucocorticoid activity.

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 35 ng/mL are reached at about

1 to 2 hours after single ingestion. Bioavailability is between 76 and 85 %. It has been reported that the intake of food had no influence on the extent of absorption of drospirenone, but the maximum concentration was reduced in comparison to intake on an empty stomach.

Distribution

After oral administration, serum drospirenone levels decrease in two phases which are characterised by half lives of 1,6 ± 0,7 hours and 27,0 ± 7,5 hours, respectively. Drospirenone is reported to bind 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 active substance concentrations are present as free steroid. The ethinyl estradiol-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 reported to be extensively metabolised after oral administration. 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-sulfate, both of which are formed without involvement of the P450 system. 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*.

Elimination

The metabolic clearance rate of drospirenone in serum is reported to be 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 reported to be reached between 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 (creatinine clearance CLcr, 50 to 80 mL/min) were reported to be comparable to those of women with normal renal function (CLcr, > 80 mL/min). The serum drospirenone levels were reported to be 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 reported to be comparable to those of women with normal hepatic function during the absorption/ distribution phases, with similar C_{max} values. The decline in serum drospirenone concentrations during the terminal disposition phase was reported to be about 1,8 times greater for the volunteers with moderate hepatic impairment 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 reported to be rapidly and completely absorbed. Peak serum concentrations of about 88 to 100 pg/mL are reached within 1 to 2 hours after single oral administration. Absolute bioavailability as a result of pre-systemic conjugation and first-pass metabolism is reported to be approximately 60 %. Concomitant intake of food has been reported to reduce the bioavailability of ethinyl estradiol in about 25 % of the investigated subjects while the maximum concentration was reduced in all subjects.

Distribution

Serum ethinyl estradiol levels decrease in two phases; the terminal disposition phase is characterised by a half-life of approximately 24 hours. Ethinyl estradiol is reported to be highly but non-specifically bound to serum albumin (approximately 98,5 %) and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 5 L/kg was determined.

Biotransformation

Ethinyl estradiol is subject to pre-systemic 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 metabolic clearance rate of ethinyl estradiol is reported to be about 5 mL/min/kg.

Elimination

Ethinyl estradiol is not excreted in unchanged form to any significant extent. The metabolites of ethinyl estradiol 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 reported to be reached during the second half of a treatment cycle and serum levels of ethinyl estradiol accumulate by a factor of about 1,4 to 2,1.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Active film-coated tablets (pink)

- ***Tablet core***
  - Lactose monohydrate
  - Pregelatinised starch (maize)
  - Povidone K-30 (E1201)
  - Croscarmellose sodium
  - Polysorbate 80
  - Magnesium stearate (E572)
- ***Tablet film-coating***
  - Polyvinyl alcohol partial hydrolysed
  - Titanium dioxide (E171)
  - Macrogol 3350
  - Talc
  - Yellow iron oxide (E172)
  - Red iron oxide (E172)
  - Black iron oxide (E172)

Inactive film-coated tablets (white)

- ***Tablet core***
    - Lactose anhydrous
    - Povidone K-30 (E1201)
    - Magnesium stearate (E572)

- ***Tablet film-coating***
    - Polyvinyl alcohol partial hydrolysed
    - Titanium dioxide (E171)
    - Macrogol 3350
    - Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Keep the blister in the outer carton until required for use.

Store at or below 25 °C.

6.5 Nature and contents of container

Carton containing one blister strip with 28 tablets. Blister strip consists of clear to slightly opaque transparent PVC/PVDC and dull silver coloured aluminium foil. Each blister of LEYLA contains 24 pink, active film-coated tablets in the 1st, 2nd, 3rd and 4th rows of the strip and 4 white placebo (inactive) film coated tablets in row 4.

Pack sizes:

1 x 28 film-coated tablets

3 x 28 film-coated tablets

6 x 28 film-coated tablets

13 x 28 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: +27860287835

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10. DATE OF REVISION OF THE TEXT