SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

LEXILEV 0,15 mg/0,03 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each LEXILEV active tablet contains 0,15 mg levonorgestrel and 0,03 mg ethinylestradiol.

Contains sugar (lactose monohydrate, 84,32 mg per active tablet).

Each LEXILEV placebo tablet contains sugar (lactose anhydrous, 89,50 mg).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.

LEXILEV 21 active tablets: Round, yellow, plain, biconvex film coated tablets.

LEXILEV 7 placebo tablets: Round, white, plain film coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LEXILEV is indicated for:

- fertility control in women
- control of dysfunctional uterine bleeding
- symptomatic treatment of primary dysmenorrhoea where contraception is also desired.

4.2 Posology and method of administration

Posology:

FOR CONTRACEPTION

To achieve maximum effectiveness, LEXILEV tablets must be taken as directed and at intervals not exceeding 24 hours. Patients should be instructed to take the tablets at the same time every day, preferably after the evening meal or at bedtime.

During the first cycle of administration, the patient is instructed to take one yellow tablet daily for 21 consecutive days, beginning on Day 1 of her menstrual cycle, i.e. the first day of bleeding.

One white placebo tablet is taken daily for the next 7 consecutive days. Withdrawal bleeding should usually occur 2 to 4 days after the last yellow tablet is taken.

During this first cycle, a mechanical, i.e. barrier, method of contraception should be supplemented until 14 tablets have been taken. If the tablets are begun after Day 5 or postpartum, it must be considered that ovulation and conception may have occurred before the tablets were started.

The next and all subsequent courses will begin on the day after the last package was completed, even if withdrawal bleeding has not occurred or is still in progress.
Each course of LEXILEV is thus begun on the same day of the week and follows the same schedule (21 days of yellow tablets, 7 days of white placebo tablets) as the first course.

The patient who is changing from another oral contraceptive product will begin
LEXILEV on the day she would usually start a new package of the other product.
During the first LEXILEV cycle, a mechanical, i.e. barrier, method of contraception should be used until 14 consecutive tablets have been taken.

If transient spotting or breakthrough bleeding occurs, the patient is instructed to continue the

regimen since such bleeding is usually without significance. If the bleeding is persistent or prolonged, the patient is advised to consult her doctor.

If a patient is changing from 21-day combined oral contraceptives or from a combined Every Day pill (28-day tablets):

The first tablet of LEXILEV should be taken on the first day immediately after the end of the previous oral contraceptive course.

If a patient is changing from a progestogen-only pill (POP):

The first tablet of LEXILEV should be taken on the first day of bleeding, even if a POP has already been taken on that day. The remaining progestogen-only pills should be discarded.

Post-partum and post-abortum use:

After pregnancy, oral contraception can be started 21 days after a vaginal delivery, provided that the patient is fully ambulant and there are no puerperal complications.

Additional contraceptive precautions will be required for the first 7 days of tablet taking. Since the first port-partum ovulation may precede the first bleeding, another method of contraception should be used in the interval between childbirth and the first course of tablets. After a first trimester abortion, oral contraception may be started immediately.

In the not breastfeeding mother, LEXILEV may be begun immediately after delivery or at the first postpartum examination, whether or not menstruation has resumed.

Missed Tablets

The patient should be instructed to take a missed yellow tablet as soon as it is remembered. If two consecutive yellow tablets are missed, they should both be taken as soon as remembered. In either case, the next tablet should be taken at its usual time. Each time the patient misses one or two consecutive yellow tablets, a mechanical method of contraception should be supplemented until 14 consecutive daily tablets have been taken or until the package is finished if less than 14 yellow tablets remain.

If the patient misses one or more placebo tablets, she is still protected against pregnancy, provided she begins the yellow tablets on the proper day. If three consecutive yellow tablets are missed, LEXILEV should be discontinued and the remainder of the package discarded. A new package should be started on the eighth day after the last tablet was taken. A mechanical method of contraception should be used until 14 consecutive daily tablets have been taken.

If withdrawal bleeding does not occur and LEXILEV has been taken according to directions, it is unlikely that the patient has conceived. She should be instructed to begin a second course of LEXILEV on the usual day. If bleeding does not occur at the end of this second cycle, LEXILEV should not be taken until diagnostic procedures to exclude the possibility of pregnancy have been performed.

If the patient has not adhered to the prescribed regimen (missed one or more yellow tablets or started taking them on a day later than recommended), the probability of pregnancy should be considered at the time of the first missed period before LEXILEV is resumed.

Gastrointestinal upset:

Vomiting or diarrhoea may reduce the efficacy of LEXILEV by preventing full absorption. If vomiting or diarrhoea occurs within 4 hours of taking LEXILEV tablet-taking from the current pack should be continued.

Additional non-hormonal methods of contraception (except the rhythm or temperature method) should be used during the gastrointestinal upset and for 7 days following the upset. If these 7 days overrun the end of a pack, the next pack should be started without a break.

In this situation, a withdrawal bleed should not be expected until the end of the second pack.

If the patient does not have a withdrawal bleed during the tablet-free interval following the end of the second pack, the possibility of pregnancy must be ruled out before starting the next pack. Other methods of contraception should be considered if the gastrointestinal disorder is likely to be

prolonged.

FOR THE SYMPTOMATIC TREATMENT OF PRIMARY DYSMENORRHOEA AND CASES OF DYSFUNCTIONAL UTERINE BLEEDING - Dosage as for contraception.

Method of administration:

For oral administration.

4.3 Contraindications

LEXILEV is contraindicated in:

- patients with hypersensitivity to ethinylestradiol or levonorgestrel or to any of the excipients in LEXILEV (see section 6.1)
- personal and family history of breast cancer
- patients known with inherited genetic mutations: BRCA1 and BRCA2 genes
- early menstrual periods (before the age of 12 years)
- history of non-cancerous breast diseases (atypical hyperplasia or lobular carcinoma in situ)
- previous treatment using radiation therapy to the chest or breast
- previous exposure to diethylstilbestrol (DES)
- concomitant use with ritonavir
- patients with recurrent cholestatic jaundice, or impaired liver function
- known or suspected estrogen-dependent neoplasia
- thrombophlebitis or thromboembolic disorders, or a history thereof
- inherited thrombophilia
- severe migraine
- cerebrovascular insufficiency
- coronary-artery disease
- undiagnosed vaginal bleeding
- patients where migraine becomes focal or when there is a loss of vision, or if there is an onset of unexplained chest pain. Medication should be discontinued immediately upon onset

of these symptoms

- known or suspected carcinoma of the breast
- benign or malignant liver tumours which developed during the use of oral contraceptives or estrogen-containing products
- active liver disease
- the presence or history of severe hepatic disease, e.g. active viral hepatitis and severe cirrhosis, as long as liver function values have not returned to normal
- previous pulmonary embolism
- previous proven deep-vein thrombosis (DVT)
- the 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)
- the 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

  - a high risk of arterial thromboembolism due to multiple risk factors or the presence of one serious risk factor such as:
    - diabetes mellitus with vascular symptoms
    - severe hypertension
    - severe dyslipoproteinaemia.
- relative contraindications include
  - a history of diabetes mellitus
  - epilepsy
  - asthma
  - hypertension
  - depression (see section 4.4)
  - porphyria
  - Dubin Johnson's syndrome
  - Rotor syndrome
  - or states in which fluid retention occur.
- pregnancy and lactation.

4.4 Special warnings and precautions for use

CIGARETTE SMOKING

CIGARETTE SMOKING INCREASES THE RISK OF SERIOUS CARDIOVASCULAR SIDE EFFECTS FROM THE USE OF LEXILEV. THE RISK INCREASES WITH AGE AND WITH HEAVY SMOKING (15 OR MORE CIGARETTES PER DAY) AND IS MARKED IN WOMEN OVER 35 YEARS OF AGE. WOMEN WHO USE ORAL CONTRACEPTIVES SUCH AS LEXILEV SHOULD BE STRONGLY ADVISED NOT TO SMOKE.

UNDER NO CIRCUMSTANCES SHOULD THE ORAL CONTRACEPTIVE TABLET BE STOPPED WITHOUT HAVING ADOPTED A SATISFACTORY ALTERNATIVE METHOD OF CONTRACEPTION.

Missed tablets – See section 4.2.

If any of the conditions or risk factors mentioned below are present, the suitability of LEXILEV 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 LEXILEV should be discontinued.

Ocular Lesions

Discontinue LEXILEV and institute appropriate diagnostic and therapeutic measures if there is a gradual or sudden, partial or complete loss of vision, proptosis or diplopia, papilloedema, or any evidence of retinal vascular lesions or optic neuritis.

Carcinoma

Ovarian, endometrial, cervical and breast cancer have been reported in women using combined oral contraceptives such as LEXILEV. Data suggests that long-term continuous administration of either natural or synthetic estrogen increases the frequency of carcinoma of the breast, cervix, vagina and liver. Under the influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.

Close clinical surveillance is essential in all women taking these preparations. In all cases of undiagnosed, persistent, or recurrent vaginal bleeding, appropriate diagnostic measures should be taken to eliminate the possibility of malignancy.
Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care.

Breast cancer

LEXILEV contains estrogen and progestogen which, on prolonged use, may increase the risk of developing breast cancer. A meta-analysis of prospective epidemiological studies from 1992 to 2018 reported a significant increase in the risk of developing breast cancer in 55,575 women 40 - 59 years

of age who used menopausal hormone therapy (MHT). The risk increased steadily with duration of use and was slightly greater for estrogen-progestogen than oestrogen only preparations, and the risk persisted for more than 10 years after stopping the treatment. The relative risk (RR) to develop breast cancer for estrogen-progestogen preparations was 1.60 at 1 - 4 years and RR = 2.08 at 5 - 14 years, while that for estrogen only preparations was 1.17 at 1 - 4 years and 1.33 at 5 - 14 years. There was no risk to develop breast cancer in women who started MHT at 60 years of age. All women on LEXILEV should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations.
Mammography evaluations should be done based on patient age, risk factors, and prior mammogram results.

Cervical cancer

The most important risk factor for cervical cancer is persistent HPV infection. Long-term use of COCs, such as LEXILEV, may further contribute to this increased risk.

Liver cancer

Benign and malignant hepatic adenomas have been found to be associated with the use of oral contraceptives such as LEXILEV. Hepatic adenomas may rupture and cause death through intra-abdominal haemorrhage. This has been reported in short- and long-term users of oral contraceptives. Such lesions may present as an abdominal mass or with signs and symptoms of an acute abdomen and should be considered if the patient has abdominal pain and tenderness, liver enlargement or evidence of intra-abdominal bleeding. LEXILEV should be discontinued if persistent upper abdominal pain develops.

Headache

The onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of LEXILEV and evaluation of the cause.

Use during or immediately preceding pregnancy

Serum folate levels may be depressed by oral contraceptives' use. Women who become pregnant shortly after discontinuing these medicines may have a greater chance of developing folate deficiency and its complications.

Foetal abnormalities, including heart defects and limb defects, have been reported in offspring of women who have taken oral contraceptives in early pregnancy.
Pregnancy should be ruled out before LEXILEV is begun and considered in women who have missed two consecutive menstrual periods. The possibility of pregnancy should be considered at the first missed menstrual period in a patient who has not adhered to the prescribed regimen.

Further oral contraceptive use should be withheld until pregnancy has been ruled out. In women who discontinue oral contraceptives with the intent of becoming pregnant, a non-hormonal method of contraception is recommended for 3 months before attempting to conceive.

Female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestins are effective for these uses.

The administration of progestin-only or estrogen-progestin combinations to induce withdrawal bleeding should not be used as a test for pregnancy.

The following conditions have been reported to occur or deteriorate with COC use.
Consideration should be given to stopping LEXILEV if any of the following occur during use:

- cholestatic jaundice has been reported in users of LEXILEV. If this occurs, this product should be discontinued. Patients with a history of jaundice during pregnancy should be carefully observed during LEXILEV therapy
- pruritus related to cholestasis

- LEXILEV may increase the risk of gallstone formation and may worsen existing disease
- systemic lupus erythematosus
- herpes gestationis
- otosclerosis-related hearing loss
- sickle cell anaemia
- renal dysfunction
- hereditary angioedema
- any other condition an individual woman has experienced worsening of during pregnancy or previous use of COCs.

Ectopic Pregnancy

Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

Bleeding Irregularities

Breakthrough bleeding, spotting and amenorrhoea are frequent reasons for patients discontinuing LEXILEV. The incidence is in the order of 1 % of users.

In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, non-functional causes should be borne in mind. In undiagnosed persistent or recurrent bleeding from the vagina, appropriate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem.

Changing to a regimen with a higher estrogen content, while potentially useful in minimising menstrual irregularity, should be done only if necessary, since this may increase the risk of thromboembolic disease.

Women with a history of oligomenorrhoea or secondary amenorrhoea or young women without regular cycles may have a tendency to remain anovulatory or to become

amenorrhoeic after discontinuation of LEXILEV. Women with these pre-existing problems should be advised of this possibility and encouraged to use another method of contraception. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

Menstrual changes

- *reduction of menstrual flow:*
  - this is not abnormal and it is to be expected. It may be beneficial where heavy periods were previously experienced
- *missed menstruation:*
  - occasionally, withdrawal bleeding may not occur at all. If the tablets have been taken correctly, pregnancy is unlikely. If withdrawal bleeding fails to occur at the end of a second pack, the possibility of pregnancy must be ruled out before resuming with the next pack
- *intermenstrual bleeding:*
  - 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. This may include curettage.

Thromboembolic Disorders

Risk of venous thromboembolism (VTE):

The use of any combined oral contraceptive (COC) such as LEXILEV increases the risk of venous

thromboembolism (VTE) compared with no use. Products that contain levonorgestrel, such as LEXILEV, norgestimate or norethisterone are associated with the lowest risk of VTE.

The decision to use LEXILEV should be taken after a discussion with the woman to ensure she understands the risk of VTE with LEXILEV, how her current risk factors influence this risk, and that her VTE risk is highest in the first ever year of use. There is also some evidence that the risk is increased when a COC is re-started after a break in use of 4 weeks or more. Thrombosis has been reported to occur in COC users in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries.

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

Risk factors for VTE:

The risk for venous thromboembolic complications in COC users may increase substantially in a woman with additional risk factors; particularly if there are multiple risk factors (see Table 1). LEXILEV is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a COC should not be prescribed (see section 4.3).

Table 1: Risk factors for VTE

Risk factor	**Comment**
Obesity (body mass index over 30 kg/m^2)	Risk increases substantially as BMI rises. Particularly important to consider if other risk factors also

	present.
Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma *Note:* temporary immobilisation including air travel > 4 hours can also be a risk factor for VTE, particularly in women with other risk factors.	In these situations it is advisable to discontinue use of LEXILEV (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 LEXILEV has not been discontinued in advance.
Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50 years).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use.
Other medical conditions associated with VTE.	Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.
Increasing age	Particularly above 35 years.

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

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

Symptoms of VTE (deep vein thrombosis and pulmonary embolism):

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

Symptoms of deep vein thrombosis (DVT) can include:

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

Symptoms of pulmonary embolism (PE) can include:

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

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

Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discolouration of an extremity. If the occlusion occurs in the eye, symptoms can range from painless blurring of vision which can progress to loss of vision.

Sometimes loss of vision can occur almost immediately.

Risk of arterial thromboembolism (ATE):

The use of COCs such as LEXILEV, is associated with an increased risk for arterial thromboembolism (myocardial infarction) or for cerebrovascular accident (e.g. transient ischaemic attack, stroke). Arterial thromboembolic events may be fatal.

Risk factors for ATE:

The risk of arterial thromboembolic complications or of a cerebrovascular accident in COC users increases in women with risk factors (see Table 2). LEXILEV is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis (see section 4.3).

If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative, LEXILEV should not be prescribed (see section 4.3).

Table 2: Risk factors for ATE

Risk factor	**Comment**
Increasing age.	Particularly above 35 years.
Smoking.	Women should be advised not to smoke if they wish to use LEXILEV. Women over 35 who continue to smoke should be strongly advised to use a different method of contraception.
Hypertension.	
Obesity (body mass index (BMI) over 30 kg/m^2).	Risk increases substantially as BMI increases. Particularly important in women with additional risk factors.

Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g. below 50 years).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use.
Migraine.	An increase in frequency or severity of migraine during LEXILEV use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation.
Other medical conditions associated with adverse vascular events.	Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus.

Symptoms of ATE:

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

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.

Reasons for stopping oral contraception immediately:

1. Occurrence for the first time, or exacerbation, of migrainous headaches or unusually frequent or unusually severe headaches.
2. Sudden disturbances of vision, of hearing or other perceptual disorders.
3. First signs of thrombosis or blood clots (e.g. unusual pains in or swelling of the leg(s), stabbing pains on breathing or coughing for no apparent reason).
   Feeling of pain and tightness in the chest.
4. At least 4 weeks before an elective major operation (e.g. abdominal, orthopaedic), any surgery to the legs, medical treatment for varicose veins or prolonged immobilisation, e.g. after accidents or surgery. Do not restart until 2 weeks after full ambulation. In case of emergency surgery, thrombotic prophylaxis is usually indicated e.g. subcutaneous heparin.
5. Onset of jaundice, hepatitis, itching of the whole body.
6. Significant rise in blood pressure.
7. Severe upper abdominal pain or liver enlargement.
8. Clear exacerbation of conditions known to be capable of deteriorating

during oral contraception or pregnancy.

Other conditions

Certain chronic diseases may deteriorate during the use of combined oral contraceptives such as LEXILEV.

Myocardial infarction and coronary artery disease

An increased risk of myocardial infarction associated with the use of oral contraceptives has been reported. Studies found that the greater the number of underlying risk factors for coronary-artery disease (cigarette smoking, hypertension, hypercholesterolaemia, obesity, diabetes, history of pre-eclampsia), the higher the risk of developing myocardial infarction. Oral contraceptives were found to be a clear additional risk factor.

Carbohydrate and lipid metabolic effects

A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives such as LEXILEV. For this reason, prediabetic and diabetic patients should be carefully observed while receiving LEXILEV. An increase in triglycerides and total phospholipids has been observed in patients receiving LEXILEV**.**

Diabetes (without vascular involvement)

Insulin-dependent diabetics without vascular disease can use LEXILEV. However it should be remembered that all diabetics are at an increased risk of arterial disease and this should be considered when prescribing LEXILEV. Diabetics with existing vascular disease are contraindicated from using LEXILEV (see section 4.3). Although LEXILEV may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs, such as LEXILEV (containing < 0,05 mg ethinylestradiol). However, diabetic women should be carefully observed while taking LEXILEV.

Strict medical supervision is required with diabetes mellitus with mild vascular disease or mild nephropathy, retinopathy or neuropathy.

Known hyperlipidaemias

Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs such as LEXILEV. Women with hyperlipidaemias are at an increased risk of arterial disease (see Risk of arterial thromboembolism (ATE)).

Blood Pressure

Hypertension is a risk factor for stroke and myocardial infarction (see section 4.4 - Risk of arterial thromboembolism (ATE)). In some women, hypertension may occur within a few months of beginning use. In the first year of use, the prevalence of women with hypertension is low but the incidence increases with increasing exposure. Age is also strongly correlated with the development of hypertension in oral contraceptive users.

Women who previously have had hypertension during pregnancy may be more likely to develop an elevation of blood pressure when given LEXILEV. If hypertension develops during the use of LEXILEV, antihypertensive treatment should normally be initiated at a blood pressure level of 160/100 mm Hg in uncomplicated patients or at 140/90 mm Hg in those with target organ damage, established cardiovascular disease, diabetes or with increased cardiovascular risk factors. Strict medical supervision is required.

Decisions about the continued use of LEXILEV should be made and alternative contraception may be advised. Hypertension that develops as a result of taking LEXILEV usually returns to normal after discontinuing LEXILEV.

Angioedema

Exogenous oestrogens may induce or exacerbate symptoms of hereditary and acquired

angioedema.

Disturbances of liver function

Acute or chronic disturbances of liver function may necessitate the discontinuation of LEXILEV use until markers of liver function return to normal. Steroid hormones may be poorly metabolised in patients with impaired liver function and should be administered with caution to such patients.

Recurrence of cholestatic jaundice and/or cholestasis-related pruritus which occurred during pregnancy or previous use of sex steroids necessitates the discontinuation of LEXILEV.

Chloasma

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 LEXILEV.

Gallbladder disease

Studies report an increased risk of surgically confirmed gallbladder disease in users of estrogens and oral contraceptives.

Psychiatric disorders

Mood changes and depression are side effects reported with the use of hormonal contraceptives including LEXILEV. There is some evidence that hormonal contraceptive use may be associated with severe depression and a higher risk of suicidal thoughts/behaviour (e.g. talking about suicide, withdrawing from social contact, having mood swings, being preoccupied with death or violence, feeling hopeless about a situation, increasing use of alcohol/drugs, doing self-destructive things, personality changes) and suicide. Prescribers should inform their patients to contact their doctor for advice if they experience mood changes and depression whilst on treatment

with LEXILEV.

Reduced efficacy

The efficacy of LEXILEV may be reduced, in the event of missed tablets, vomiting or diarrhoea, or concomitant medication (see section 4.3).

ALT elevations

Patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). ALT elevations have also been observed with HCV anti-viral medicinal products containing glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir (see sections 4.3 and 4.5).

Medical examination/consultation

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

Laboratory tests and investigations should include but not be limited to Papanicolaou smears, blood glucose levels, liver- and kidney function tests, and monitoring of existing conditions. The frequency and nature of these assessments should be based upon relevant guidelines and should be adapted to the individual woman, but should include measurement of blood pressure and breast, abdominal and pelvic examination including cervical cytology.

Patient education should include: recognition of VTE and ATE symptoms and associated risk factors,

that hormonal contraceptives do not protect against contracting HIV and other sexually transmitted diseases, informing a medical practitioner of LEXILEV use prior a major surgery and reporting of worsening of existing medical conditions or side effects.

Porphyria

Safety has not been established. Strict medical supervision is required.

Excipient warnings:

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

4.5 Interaction with other medicines and other forms of interaction

Hepatic enzyme inducers

Medicines which induce hepatic enzymes (especially cytochrome P450 3A4) increase the metabolism of LEXILEV and hence may result in breakthrough bleeding and/or contraceptive failure (pregnancy). The following have been shown to have clinically important interactions with LEXILEV:

Antiretroviral medicines:

- ritonavir
- nelfinavir
- nevirapine.

Note: There are other antiretroviral medicines that may increase plasma concentration of sex hormones.

Anticonvulsants:

- barbiturates (including phenobarbitone)
- primidone

- phenytoin
- carbamazepine
- oxcarbazepine
- topiramate
- felbamate.

Antibiotics/antifungals:

Women on short-term treatment with these antibiotics must temporarily use a barrier contraceptive method concomitantly with the contraceptive tablets. Oral contraceptive failure may occur with concomitant antibiotic therapy. For maximal protection, additional non-hormonal contraception is recommended for the duration of antibiotic therapy and for seven days thereafter. Those on long-term antibiotic therapy need only take extra precautions for the first two weeks of antibiotic therapy. Spotting and breakthrough bleeding are possible signs of diminished contraceptive effectiveness.

- griseofulvin
- ampicillin
- penicillin v
- tetracycline
- rifampicin
- neomycin
- chloramphenicol
- sulphonamides
- nitrofurantoin.

Herbal remedies

- St. John’s wort (*Hypericum perforatum*).

Managing interactions with hepatic enzyme inducers:

Interactions can occur with medicines that induce microsomal enzymes which can result in increased clearance of LEXILEV, which may lead to breakthrough bleeding and/or contraceptive failure. Women on short term treatment with any of these medicines should temporarily use a barrier method in addition to the COC or choose another method of contraception.

The barrier contraceptive method should be used during the time of concomitant medicine administration and for 28 days after their discontinuation. If the period during which the barrier method used runs beyond the last active (yellow) tablet, the user should finish taking all the active tablets, discard the placebo (white) tablets and start a new pack of LEXILEV the next day with an appropriate active tablet. In this situation, a withdrawal bleed should not be expected until the end of the second pack. If the patient does not have a withdrawal bleed during the tablet free interval following the end of the second pack, the possibility of pregnancy must be ruled out before resuming with the next pack.

For women receiving long-term therapy with hepatic enzyme inducers, another method of contraception should be used.

Medicines increasing the clearance of COCs such as LEXILEV (diminished efficacy of COCs by enzyme-induction):

Phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John's wort.

Medicines decreasing the clearance of COCs (enzyme inhibitors):

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole), and macrolides (e.g. erythromycin) can increase plasma concentrations of the estrogen or the progestin or both.

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

Substances with variable effects on the clearance of COCs, e.g.: When co-administered with LEXILEV:

Many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of estrogen or progestin. These changes may be clinically relevant in some cases.

Effects on other medicines:

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

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

Pharmacodynamic interactions

Concomitant use with medicines containing ombitasvir/paritaprevir/ritonavir, dasabuvir, with or without ribavirin, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir, may increase the risk of ALT elevations (see section 4.4).

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

Laboratory tests

The use of LEXILEV 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. Laboratory staff should therefore be informed about LEXILEV use when laboratory tests are requested.

- increased prothrombin and Factors VII, VIII, IX and X; decreased anti-thrombin-III; increased noradrenaline-induced platelet aggregation
- increased thyroid-binding globulin (ITBG) leading to increased circulating total-thyroid hormone, as measured by protein bound iodine (PBI), T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered
- decreased pregnanediol excretion
- reduced response to metyrapone test
- increased sulphobromophthalein retention.

The results of these tests should not be regarded as reliable until LEXILEV use has been discontinued for 1 to 2 months. Abnormal tests should then be repeated. LEXILEV may produce false positive results when neutrophil alkaline phosphatase activity is evaluated for the early diagnosis of pregnancy.

A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. For this reason diabetic patients should be carefully observed while on LEXILEV therapy.

4.6 Fertility, pregnancy and lactation

LEXILEV use is contraindicated in pregnancy and lactation (see section 4.3).

Pregnancy:

If pregnancy occurs during treatment with LEXILEV, further intake must be stopped immediately.

Foetal abnormalities including heart defects and limb defects, have been reported in offspring of women who have taken oral contraceptive in early pregnancy (see section 4.4). The increased risk of VTE during the postpartum period should be considered when re-starting LEXILEV.

The decision to prescribe LEXILEV should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE).

Breastfeeding:

Mothers taking LEXILEV should not breastfeed their infants (see section 4.3). The use of LEXILEV during lactation may lead to a reduction in the volume of milk produced and to a change in its composition. The active substances are excreted with the milk. These amounts may affect the child particularly in the first 6 weeks postpartum. Mothers who are breastfeeding their infants are advised to use another method of contraception.

Fertility:

No data available.

4.7 Effects on ability to drive and use machines

Since adverse reactions such as dizziness have been reported in patients receiving LEXILEV patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that LEXILEV does not adversely affect their ability to do so (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions with LEXILEV are nausea, abdominal pain, increased weight, headache, depressed mood, altered mood, breast pain, breast tenderness. Serious adverse reactions are arterial and venous thromboembolism.

Tabulated list of adverse reactions

System Organ Class	**Frequency**	**Side effects**
Infections and infestations	*Frequent*	Vaginitis, including candidiasis
Neoplasms benign and malignant (including cysts and polyps)	*Less frequent*	Liver tumours (benign and malignant), breast cancer, cervical cancer
Immune system disorders	*Less frequent*	Hypersensitivity, exacerbation of hereditary angioedema
Metabolism and nutrition disorders	*Less frequent* *Frequency unknown*	Hypertrigliceridaemia, changes in appetite Precipitation of acute attack of porphyria
Psychiatric disorders	*Frequent*	Depressed mood, altered mood, nervousness, decreased libido, increased libido
Nervous systemdisorders	*Frequent* *Less frequent*	Headache, migraine Exacerbation of chorea, dizziness
Eye disorders	*Less frequent*	Changes in corneal curvature (steepening), intolerance to contact lenses, cataracts

Cardiac disorders	*Less frequent*	An increased risk of myocardial infarction
Vascular disorders	*Less frequent*	Hypertension, venous thromboembolism (VTE), arterial thromboembolism (ATE). An increased risk of arterial and venous thrombotic and thrombo-embolic events, including stroke (e.g. ischaemic stroke, haemorrhagic stroke), transient ischaemic attacks, venous thrombosis and pulmonary embolism
Gastrointestinal disorders	*Frequent* *Less frequent*	Nausea, abdominal pain, vomiting Diarrhoea, Crohn's disease, ulcerative colitis, abdominal cramps, bloating, gastrointestinal irritation and pancreatitis
Hepato-biliary disorders	*Less frequent*	Liver function disturbances, gallbladder disease, cholestatic jaundice, exacerbation of existing

		disease
Skin and subcutaneous tissue disorders	*Frequent* *Less frequent* *Frequency unknown*	Acne Rash, urticarial erythema nodosum, erythema multiforme, chloasma or melasma which may be persistent, skin pigmentation Hirsutism, loss of scalp hair, haemorrhagic eruption
Musculoskeletal and connective tissue disorders	*Less frequent*	Systemic lupus erythematosus
Renal and urinary disorders	*Frequency unknown*	Cystitis like syndrome, haemolytic uremic syndrome
Reproductive system and breast disorders	*Frequent* *Less frequent*	Breast pain, breast tenderness, spotting, breakthrough bleeding, breast hypertrophy, breast secretion Vaginal discharge, reduced menstrual flow, missed withdrawal bleeding, post pill amenorrhoea, change

		in cervical erosion or cervical secretion, premenstrual-like syndrome
General disorders and administration site conditions	*Frequent*	Fluid retention/oedema
Investigations	*Frequent* *Less frequent*	Changes in weight (increase or decrease) Changes in serum lipid levels

Post-marketing side effects

The following side effects have been reported with the post-marketing use of oestrogen and/or progesterone/progestogen containing medicines:

Psychiatric disorders

Frequency unknown: Severe depression with a higher risk of suicidal thoughts/behaviour and suicide.

Reporting of suspected adverse reactions:

Reporting of 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 online service for adverse drug reaction reporting by using either of the following links:

https://www.sahpra.org.za/Publications/Index/8 or http://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 Overdose

Symptoms

Overdosage may cause nausea and vomiting and withdrawal bleeding may occur in females.

Treatment

Treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Progestogens and estrogens, fixed combinations.

ATC Code: G03AA07

Pharmacological classification: A 18.8 Ovulation controlling agents.

Oral contraceptives of the combination type act by a multiplicity of mechanisms.
Ovulation is inhibited by suppression of gonadotropin release, particularly the mid-cycle peaks and the viscosity of the cervical mucous is increased, impairing sperm penetration, and an endometrium less receptive for implantation is formed.

5.2 Pharmacokinetic Properties

Absorption

Ethinylestradiol and levonorgestrel are well absorbed from the gastrointestinal tract.
Ethinylestradiol is subject to considerable first-pass metabolism with a mean bioavailability of 40 to 45 %. Levonorgestrel does not undergo first-pass metabolism and is therefore completely bioavailable.

Distribution

Levonorgestrel is extensively plasma protein bound both to sex hormone binding globulin (SHBG) and albumin. Ethinylestradiol, however, is bound in plasma only to albumin and enhances the binding capacity of SHBG. Following oral administration, peak plasma levels of each medicine occur within 1 to 4 hours.

Metabolism

Ethinylestradiol is primarily metabolised by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present both free and as conjugates with glucuronide and sulphate.

Levonorgestrel is primarily metabolised by reduction of the A ring followed by glucuronidation.

Elimination

The elimination half-life for ethinylestradiol is approximately 25 hours. Conjugated ethinylestradiol is excreted in bile and subject to enterohepatic recirculation. About 40 % of ethinylestradiol is excreted in the urine and 60 % is eliminated in the faeces. The elimination half-life for levonorgestrel is approximately 24 hours. About 60 % of levonorgestrel is excreted in the urine and 40 % is eliminated in the faeces.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

LEXILEV active tablets:

Crospovidone

Lactose monohydrate

Magnesium stearate

Povidone K30

LEXILEV active tablet coating:

Iron Oxide Yellow

Macrogol

Polyvinyl alcohol

Talc

Titanium dioxide

LEXILEV placebo tablets:

Lactose anhydrous

Magnesium stearate

Povidone K30

LEXILEV placebo tablet coating:

Opadry® II White (containing macrogol, polyvinyl alcohol, talc, titanium dioxide).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep blister in the outer carton.

6.5 Nature and contents of container

PVC-PVDC/aluminium push-through foil blister strip.

Blister strip is packed into an outer carton.

Pack size: 21 active and 7 placebo film coated tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor Grapevine House,

Steenberg Office Park, Silverwood Close,

Westlake, 7945,

Cape Town, South Africa

8. REGISTRATION NUMBERS

A52/18.8/1022

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 04 August 2022

10. DATE OF REVISION OF THE TEXT

07 May 2024