LEAFLET
P031
KEYLINE VERSION :
A / 22.01.2024
DIMENSIONS **(SCALE 100 %)**:
222 x 510 ± 1 mm
SITE:
LEÓN FARMA

CHEMO
Global Affinity in Healthcare

MATERIAL INFORMATION

CAUSE:
○ LAUNCH ○ CUSTOMER CHANGE ● INTERNAL CHANGE ○ MOCKUP

MATERIAL CODE: **919861-01 PR DR/EE LIZELLE3-0,02MG X21 EURODRUG MY**

VERSION: **A** DATE: **30.09.25** PREVIOUS CODE: **588288**

LAETUS: **57060** OBSERVATIONS: -

57060

TECHNICAL SPECIFICATIONS

FOLDED:
○ NO ● YES FOLDED DIMENSIONS: **FOLD TO 170 X 37 MM**
OTHER FINISH (IF NOT SPECIFY): ______

PANTONES: ONLY A MAX. OF 6 PRINTING COLORS / PLEASE, INDICATE BELOW THE COLOURS TO BE USED
PRINTING COLOURS / **FRONT SIDE**
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PRINTING COLOURS / **BACK SIDE**
BLACK
TECHNICAL COLOURS (NO PRINTING COLOURS)
DIE CUT | FINAL FOLDED | SECURITY MARGINS

APPROVAL

DRAWED BY: (CHEMO ARTWORK TECHNICIAN) **Manuel Mancilla**
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FRONT SIDE

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LAETUS CENTERED WITHIN FINAL FOLDED 37 mm

510 mm
490 mm
10 mm

Page 1

LIZELLE 0.02mg/3mg film-coated tablet

QUALITATIVE AND QUANTITATIVE COMPOSITION

21 pink/peach film-coated tablets:
Each film-coated tablet contains 0.02 mg of ethinylestradiol and 3 mg of drospirenone
Excipient: Lactose monohydrate 44 mg

PHARMACEUTICAL FORM

Round, pink/peach film coated tablet.

CLINICAL PARTICULARS

Therapeutic indications

Oral contraception.

Posology and method of administration

For oral administration
The tablets must be taken every day at about the same time, if necessary with a little liquid in the order shown on blister pack. **LIZELLE 0.02mg/3mg film-coated tablet**:
One tablet is to be taken daily for 21 consecutive days. Each subsequent pack is started after 7-day tablet-free interval, during which time withdrawal bleed occurs. This usually starts on day 2-3 after the last tablet and may not have finished before the next pack is started.

- 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).

- Changing from a combined hormonal contraceptive combined oral contraceptive (COC)
  The woman should start **LIZELLE 0.02mg/3mg film-coated tablet** on the day following the usual hormone free interval (tablet-free or placebo tablet interval) of her previous combined oral contraceptive method. In case a vaginal ring or transdermal patch has been used the woman should start using **LIZELLE 0.02mg/3mg film-coated tablet** preferably on the day of removal, but at the latest when the next application would have been due.

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

- Following first trimester abortion.
  The woman may start immediately. When doing so, she need not take additional contraceptive measures.

- Following delivery or second-trimester abortion
  Woman should be advised to start at day 21 to 28 after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period. For breastfeeding women see Section Pregnancy & Lactation.

Management of missed tablets
The following advice only refers to missed active tablets (rows 1- 3 of the blister):
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 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. tablet-taking must never be discontinued for longer than 4 consecutive days.
2. 7 days of uninterrupted tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian- axis.
   Accordingly the following advice can be given in daily practice:

- **Week 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 the remaining tablets at her usual time. In addition, a barrier method such as condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of pregnancy should be considered. The more tablets are missed and the closer they are to the tablet-free interval, the higher the risk of a pregnancy.

- **Week 2**

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 the remaining 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 the next 7 days following the last forgotten tablet.

- **Week 3**

The risk of reduced reliability is imminent because of the forth coming 7 day tablet-free interval . However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precaution, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, she should follow the first of these two options and use extra precautions for the next 7 days as well.

1. The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at same time. She then continues to take remaining tablets at her usual time. The next blister pack must be started as soon as the current blister pack is finished i.e. no gap should be left between packs.
   The user is unlike 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 tablet-taking from the current blister pack. She should then have a tablet-free interval of up 4 days, including the days she missed tablets, and subsequently continue with the next blister pack.

If the woman missed tablets and subsequently has no withdrawal bleed in the first normal tablet –free interval, the possibility of a pregnancy should be considered.

Advise 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 3-4 hours after active tablet-taking, a new (replacement) tablet should be taken as soon as possible. The new tablet should be taken within 12 hours of the usual time of tablet- taking if possible. If more 12 hours elapse, the advice concerning missed tablets, as give in section 4.2, "Management of missed tablets", is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) from another blister strip.

How to postpone a withdrawal bleed
To delay a period the woman should continue with another blister pack of **LIZELLE 0.02mg/3mg film-coated tablet** without a tablet-free interval. 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 **LIZELLE 0.02mg/3mg film-coated tablet** is then resumed after the usual 7-days tablet-free interval.
To shift her periods to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming tablet-fee interval by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough-bleeding and spotting during subsequent pack (just as when delaying period).

Contraindications

Combined oral contraceptives (COCs) 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 COC use, the product should be stopped immediately.
- Venous thrombosis present or in history (deep venous thrombosis, pulmonary embolism).
- Arterial thrombosis present or in history (e.g. myocardial infarction) or prodromal conditions (e.g. angina pectoris and transient ischemic attack).
- Cerebrovascular accident present or in history.
- The presence of a severe or multiple risk factor(s) for arterial thrombosis.
  - Diabetes mellitus with a vascular symptoms
  - Severe hypertension
  - Severe dyslipoproteinemia
- Hereditary or acquired predisposition for venous or arterial thrombosis, such as APC-resistance, antithrombin-III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).
- Pancreatitis or history of such a condition, if associated with severe hypertriglyceridemia.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Severe renal insufficiency or acute renal failure.
- 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
- History of migraine with focal neurological symptoms
- Hypersensitivity to the active substances or to any of the excipients of **LIZELLE 0.02mg/3mg film-coated tablet**.

LIZELLE 0.02mg/3mg film-coated tablet is contraindicated for concomitant use with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir (See Section Warnings and Precautions and Section Interactions with Other Medicaments).

Special warnings and precautions for use

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

- Circulatory Disorders

The use of any combined oral contraceptive carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive.
The VTE risk of **LIZELLE 0.02mg/3mg film-coated tablet** is currently unknown.
Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in contraceptive pill users. There is no consensus as to whether the occurrence of these events is associated with the use of hormonal contraceptives.
Symptoms of venous or arterial thrombotic / thromboembolic events or of a cerebrovascular accident can include:
- unusual unilateral leg pain and/ or swelling
- sudden severe pain in the chest, whether or not it radiates to the left arm
- sudden breathlessness
- sudden onset of coughing
- any unusual, severe, prolonged headache
- sudden partial or complete loss of vision
- diplopia
- slurred speech or aphasia
- vertigo
- collapse with or without focal seizure
- weakness or very marked numbness suddenly affecting one side or one part of the body
- motor disturbances
- 'acute abdomen'.

The risk for venous thromboembolic complications in COCs users increases with:
- increasing age.
- a positive family history (venous thromboembolism ever in a sibling or parent at relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use
- prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue the pill (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Antithrombotic treatment should be considered if the pills have not been discontinued in advance
- obesity (body mass index over 30 kg/m²).
- there is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.

The risk of arterial thromboembolic complications or of a cerebrovascular accident in COC users increases with:
- increasing age.
- smoking (women over 35 years should be strongly advised not to smoke if they wish to use an COC).
- dyslipoproteinemia.
- hypertension.
- migraine.
- obesity (body mass index over 30 kg/m²)
- a positive family history (arterial thromboembolism ever in a sibling or parent at relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use
- valvular heart disease.
- atrial fibrillation.

The presence of one serious risk factor or multiple risk factors for venous or arterial disease, respectively, can also constitute a contra-indication. The possibility of anticoagulant therapy should also be taken into account. COC users should be specifically pointed out to contact their physician in case of possible symptoms of thrombosis. In case of suspected or confirmed thrombosis, COC use should be discontinued. Adequate alternative contraception should be initiated because of the teratogenicity of anticoagulant therapy (coumarins).

The increased risk of thromboembolism in the puerperium must be considered (see Section Pregnancy and Lactation).
Other medical conditions which have been associated with adverse vascular events include diabetes mellitus, systemic lupus erythematosus, haemolytic uremic syndrome and chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.
An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

- **Tumours**

An increased risk of cervical cancer in long-term users of COCs (>5 years) has been reported in some epidemiological studies, but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behaviour and other factors such as human papilloma virus (HPV).
In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of COCs. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking COCs.
With the use of the higher-dosed COCs (50 µg ehinylestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to lower-dosed COCs remains to be confirmed.

- **Other conditions**

The progestin component in **LIZELLE 0.02mg/3mg film-coated tablet** 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 medicinal products 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 pretreatment serum potassium in the upper reference range, and particularly during concomitant use of potassium sparing medicinal products. See also section Interactions with other medicinal products and other forms of interaction.
Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.
Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. Only in these rare cases an immediate discontinuation of COC use is justified. If, during the use of a COC in preexisting hypertension, constantly elevated blood pressure values or a significant increase in blood pressure do not respond adequately to antihypertensive treatment, the COC must be withdrawn. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.
The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstones; porphyria; systemic lupus erythematosus; haemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.
In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.
Acute or chronic disturbances of liver function may necessitate the discontinuation of COC 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 COCs.

Although COCs 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 (containing < 0.05 mg ethinylestradiol). However, diabetic women should be carefully observed, particularly in the early stage of COC use.

Worsening of endogenous depression, of epilepsy, of Crohn's disease and of ulcerative colitis has been reported during COC use.
Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking COCs.
Each pink/peach tablet of this medicinal product contain 44 mg lactose per tablet, the white tablet contain 89.5 mg. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose-free diet should take this amount into consideration.

Medical examination/consultation
Prior to the initiation or reinstitution of **LIZELLE 0.02mg/3mg film-coated tablet,** 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 **Contraindications**) and warnings (see **Special Warnings and special precautions for use**).The woman should also be instructed to carefully read the user leaflet and to adhere the advice given. The frequency and nature of examinations should be based on established practice guidelines and be adapted to the individual woman.
Women should be advised that oral contraceptives do not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Reduced efficacy
The efficacy of COCs may be reduced in the event of e.g. missed active tablets (see section **Posology and method of administration**), gastro- intestinal disturbances during active tablet taking (see section **Posology and method of administration**) or concomitant medication (see section **Interactions with other medicinal products and other forms of interaction**).

Reduced cycle control
With all COCs, 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 placebo tablet phase. If the COC has been taken according to the directions described in section **Posology and method of administration**, it is unlikely that the woman is pregnant.
However, if the COC 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 COC use is continued.

ALT elevations
During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir with / 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). Patients who are taking ethinylestradiol-containing medicinal products must switch to an alternative method of contraception (e.g. progestin only contraception or non-hormonal methods) prior to initiating ombitasvir / paritaprevir / ritonavir and dasabuvir therapy (See Section Contraindications and Section Interactions with Other Medicaments).

Interactions with other medicinal products and other forms of interaction

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

- Influence of other medicinal products on **LIZELLE 0.02mg/3mg film-coated tablet**

Interactions between oral contraceptives and other medicinal products may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature.

Hepatic metabolism
Interactions can occur with drugs that induce hepatic enzymes which can result in increased clearance of sex hormones e.g.phenytoin, barbiturates, primidone, carbamazepine, rifampicin, bosentan and HIV- medication (e.g ritonavir, nevirapine) and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing the herbal remedy St. John's Wort (hypericum perforatum).
Maximal enzyme induction is generally seen in about 10 days but may then be sustained for at least 4 weeks after the cessation of drug therapy.

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Page 2

Interference with Enterohepatic circulation
Contraceptive failures have also been reported with antibiotics, such as penicillins and tetracyclines. The mechanism of this effect has not been elucidated.

Management
Women on short-term treatment with any of the abovementioned classes of medicinal products or individual active substances (hepatic enzyme-inducing medicine) besides rifampicin should temporarily use a barrier method in addition to the COC, i.e. during the time of concomitant medicinal product administration and for 7 days after their discontinuation.
For women on rifampicin a barrier method should be used in addition to the COC during the time of rifampicin administration and for 28 days after its discontinuation.
In women on long-term treatment with hepatic enzyme-inducing active substances, another reliable, non-hormonal, method of contraception is recommended.
Women on treatment with antibiotics (beside rifampicin, see above) should use the barrier method until 7 days after discontinuation.
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.

- Influence of **LIZELLE 0.02mg/3mg film-coated tablet** on other medicinal products
  Oral contraceptives may affect the metabolism of certain other active substances. Accordingly, plasma and tissue concentrations may either increase (e.g. ciclosporin) or decrease (e.g. lamotrigine).
  Based on in vitro inhibition studies and in vivo interaction studies in female volunteers using omeprazole, simvastatin and midazolam as marker substrate, an interaction of drospirenone at doses of 3 mg with the metabolism of other active substances is unlikely.

- Other interactions
  In patients without renal insufficiency, the concomitant use of drospirenone and ACE-inhibitors or NSAIDs did not show a significant effect on serum potassium. Nevertheless, concomitant use of **LIZELLE 0.02mg/3mg film-coated tablet** with aldosterone antagonists or potassium-sparing diuretics has not been studied. In this case, serum potassium should be tested during the first treatment cycle. See also section **Special warnings and precautions for use**

- 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.
  Concomitant use with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (See Section Contraindications and Section Warnings and Precautions). Therefore, 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 drug regimen.
  LIZELLE 0.02mg/3mg film-coated tablet can be restarted 2 weeks following completion of treatment with this combination drug regimen.

Pregnancy and lactation

LIZELLE 0.02mg/3mg film-coated tablet is not indicated in pregnancy.
If pregnancy occurs during use of **LIZELLE 0.02mg/3mg film- coated tablet**, the preparation should be withdrawn immediately. Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were taken in advertently during pregnancy.

Animal studies have shown undesirable effects during pregnancy and lactation (see section Preclinical safety data). Based on these animal data, undesirable effects due to hormonal action of the active compounds cannot be excluded. However, general experience with COCs during pregnancy did not provide evidence for an actual undesirable effect in humans.

The available data regarding the use of **LIZELLE 0.02mg/3mg film- coated tablet** during pregnancy are too limited to permit conclusions concerning negative effects of **LIZELLE 0.02mg/3mg film-coated tablet** on pregnancy, health of the foetus or neonate. To date, no relevant epidemiological data are available.

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 breast-feeding 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.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. No effects on ability to drive and use machines have been observed in users of COCs.

Undesirable effects

For serious undesirable effects in COC users see section **Special warnings and precautions for use.**

The following adverse drug reactions have been reported during use of **LIZELLE 0.02mg/3mg film-coated tablet**. The table below reports adverse reactions by MedDRA system organ classes (MedDRA SOCs). The frequencies are based on clinical trial data. The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Adverse drug reactions which have been associated with the use of LIZELLE 0.02mg/3mg film-coated tablet as oral contraceptive or in the treatment of moderate acne vulgaris according to the MedDRA system organ classes and MedDRA terms

System Organ Class (MedDRA version 9.1)	Common	Uncommon	Rare	Not known (cannot be estimated from the available data)
Infections and infestations			Candidiasis	
Blood and lymphatic system disorders			Anemia Thrombocythemia	
Immune system disorders			Allergic reaction	Hyper-sensitivity
Endocrine disorders			Endocrine disorder	
Metabolism and nutrition disorders			Increased appetite Anorexia Hyperkalemia Hyponatremia	
Psychiatri disorders	Emotional lability	Depression Nervousness Somnolence Libido decreased	Anorgasmia Insomnia	
Nervous system disorders	Headache	Paresthesia Dizziness	Vertigo Tremor	
Eye disorders			Conjunctivitis Dry eye Eye disorder	
Cardiac disorders			Tachycardia	
Vascular disorders		Hypertension Migraine Varicose vein	Phlebitis Vascular disorder Epistaxis Syncope	
Gastro-intestinal disorders	Nausea	Abdominal pain Vomiting Dyspepsia Flatulence Gastritis Diarrhoea	Abdomen enlarged Gastrointestinal disorder Gastrointestinal fullness Hiatus hernia Oral candidiasis Constipation Dry mouth	
Hepatobiliary disorders			Biliary pain Cholecystitis	
Skin and subcutaneous tissue disorders		Acne Pruritus Rash	Chloasma Eczema Alopecia Dermatitis acneiform Dry skin Erythema nodosum Hypertrichosis Skin disorder Skin striae Contact dermatitis Photosensitive dermatitis Skin nodule	Erythema multiforme
Musculo-skeletal and connective tissue disorders		Back pain Pain in extremity Muscle cramps		
Reproductive system and breast disorders	Breast pain Metrorrhagia * Amenorrhea	Vaginal candidiasis Pelvic pain Breast enlargement Fibrocystic breast Uterine/Vaginal bleeding* Genital discharge Hot flushes Vaginitis Menstrual disorder Dysmenorrhoea Hypomenorrhea Menorrhagia Vaginal dryness Papanicolaou smear suspicious	Dyspareunia Vulvovaginitis Postcoital bleeding Withdrawal bleeding Breast cyst Breast hyperplasia Breast neoplasm Cervical polyp Endometrial atrophy Ovarian cyst Uterine enlargement	
General disorders and administration site conditions		Asthenia Sweating increased Edema (Generalized edema, peripheral edema, face edema)	Malaise	
Investigations		Weight increase	Weight decrease	

* bleeding irregularities usually subside during continued treatment

The following serious adverse events have been reported in women using COCs, which are discussed in section **Special warnings 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, migraine, 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 slightly increased among OC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. For further information, see **Contraindications** and **Special warning and precautions for use**.

Overdose

There has not yet been any experience of overdose with **LIZELLE 0.02mg/3mg film-coated tablet**. On the basis of general experience with combined oral contraceptives, symptoms that may possibly occur in case of taking an overdose of active tablets are: nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group (ATC): Progestogens and estrogens, fixed combinations.
ATC Code: G03AA12.
The contraceptive effect of **LIZELLE 0.02mg/3mg film-coated tablet** 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 endometrium.

LIZELLE 0.02mg/3mg film-coated tablet is a combined oral contraceptive with ethinylestradiol and the progestogen drospirenone. In a therapeutic dosage, drospirenone also possesses antiandrogenic and mild antimineralocorticoid properties. It has no estrogenic, glucocorticoid and antiglucocorticoid activity. This gives drospirenone a pharmacological profile closely resembling the natural hormone progesterone.
There are indications from clinical studies that the mild antimineralocorticoid properties of **LIZELLE 0.02mg/3mg film- coated tablet** result in a mild antimineralocorticoid effect.

Pharmacokinetic properties

Drospirenone

Absorption
Orally administered drospirenone is rapidly and almost completely absorbed. Maximum concentrations of the active substance in serum of about 38 ng/ml are reached at about 1-2 h after single ingestion. Bioavailability is between 76 and 85%.
Concomitant ingestion of food has no influence on the bioavailability of drospirenone.

Distribution
After oral administration, serum drospirenone levels decrease with a terminal half-life of 31 h.

Drospirenone is bound to serum albumin and does not bind to sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG). Only 3 - 5 % of the total serum concentrations of the active substance are present as free steroid. The ethinylestradiol-induced increase in SHBG does not influence the serum protein binding of drospirenone. The mean apparent volume of distribution of drospirenone is 3.7 ± 1.2 l/kg.

Metabolism
Drospirenone is extensively metabolized 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 metabolized to a minor extent 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 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 40h.

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

Special patient populations

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

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

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

Ethinylestradiol

Absorption
Orally administered ethinylestradiol is absorbed rapidly and completely.
After administration of 30 µg, peak plasma concentrations of 100 pg/mL are reached 1-2 hours after ingestion. Ethinylestradiol undergoes an extensive first-pass effect, which displays great inter-individual variation. The absolute bioavailability is approx. 45 %.

Distribution
Ethinylestradiol has an apparent volume of distribution of 5 L/kg and binding to plasma proteins is approx. 98 %. Ethinylestradiol induces the hepatic synthesis of SHBG . During treatment with 30 µg ethinylestradiol the plasma concentration of SHBG increases from 70 to about 350 nmol/L. Ethinylestradiol passes in small amounts into breast milk (0.02 % of the dose).

Metabolism
Ethinylestradiol is metabolized completely (metabolic plasma clearance 5 ml/min/kg).

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

Steady-state conditions
Steady-state conditions are reached during the second half of a treatment cycle and serum levels of ethinylestradiol accumulate by a factor of about 1.4 to 2.1

Shelf-life

18 months.

Storage

Do not store above 30ºC. Keep out of reach of children.
Jauhi daripada kanak-kanak.

Presentation

Blisters of aluminium push-thru foil and PVC/PVDC film.

It is available in a box of 21 film-coated tablets.

Manufacturer:
LABORATORIOS LEÓN FARMA, S.A.
La Vallina, s/n Polígono Industrial, Navatejera,
24193 León, Spain.

Product Registration Holder:
EURODRUG LABORATORIES (M) SDN BHD
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Jalan USJ 25/1C, 47650 Subang Jaya,
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Date of revision: 18 September 2025

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