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PROFESSIONAL INFORMATION

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SCHEDULING STATUS: S3

1 NAME OF THE MEDICINE

LOGYNON® ED

Ethinylestradiol 0,03 mg and Levonorgestrel 0,05 mg
Ethinylestradiol 0,04 mg and Levonorgestrel 0,075 mg
Ethinylestradiol 0,03 mg and Levonorgestrel 0,125 mg

Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The 28-day pack (Every-Day pack) contains 21 hormonal tablets, 6 tablets each with levonorgestrel 0,05 mg and ethinylestradiol 0,03 mg, plus 5 tablets each with levonorgestrel 0,075 mg and ethinylestradiol 0,04 mg, plus 10 tablets each with levonorgestrel 0,125 mg and ethinylestradiol 0,03 mg, plus 7 non-hormonal tablets.

Excipients with known effect: each hormonal tablet contains lactose 31 mg and each non-hormonal tablet contains lactose 34 mg.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

6 small pale brown coated hormonal tablets, 5 small white coated hormonal tablets, 10 small ochre coated hormonal tablets, and 7 large white coated non-hormonal tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indication

Oral contraception.

4.2 Posology and method of administration

Combined oral contraceptives, when taken correctly, have a failure rate of approximately 1 % per year. The failure rate may increase when pills are missed or taken incorrectly.

How to take LOGYNON ED

Tablets must be taken in the order directed by the arrows on the pack, every day at about the same time with some liquid as needed. Tablet-taking is continuous. One tablet is to be taken daily for 28 consecutive days. The first tablet should be taken from the red section of the calendar pack by selecting the appropriate tablet for that day of the week (e.g. “MO” for Monday). Each subsequent pack is started the day after the last tablet of the previous pack. Withdrawal bleeding usually starts on 2 to 3 days after starting the hormone-free

tablets and may not have finished before the next pack is started. If a patient starts LOGYNON ED during the latter part of the week, the very first cycle may be slightly shortened.

How to start LOGYNON ED

7 days of uninterrupted active tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

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). If the woman starts with an inactive tablet on day 1, she should be advised to additionally use a barrier method for the first 14 days of tablet-taking. Starting on days 2 to 5 is allowed, but during the first cycle a barrier method is recommended in addition for the first 14 days of tablet-taking.

Changing from a combined hormonal contraceptive (combined oral contraceptive/COC), vaginal ring, or transdermal patch)

The woman should start with LOGYNON ED preferably on the day after the last active tablet (the last tablet containing the active substances) of her previous combined oral contraceptive, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous combined oral contraceptive. In case a vaginal ring or transdermal patch has been used, the woman should start using LOGYNON ED preferably on the day of removal of the last ring or patch of a cycle pack, 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 on any day from the minipill (from an implant or the intrauterine system 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 14 days of tablet-taking.

Following first trimester abortion

The woman may start immediately. She should be advised to additionally use a barrier method for the first 14 days of tablet-taking.

Following delivery or second-trimester abortion

For breastfeeding women see section 4.6.

Women should be advised to start on day 21 after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 14 days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of combined oral contraceptive use or the woman has to wait for her first menstrual period.

Management of missed tablets

Missed hormone-free larger white inactive tablets can be disregarded. However, they should be discarded to avoid unintentionally prolonging the inactive hormone-free tablet phase. The following advice only refers to missed hormone-containing coated tablets.

If the user is ***less than 12 hours*** late in taking any active tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

If she is ***more than 12 hours*** late in taking any active tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

1. active tablet-taking must never be discontinued for longer than 7 days;
2. 7 days of uninterrupted active tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Accordingly, the following advice can be given in daily practice:

First 7 days of active tablet-taking

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets that are missed and the closer they are to the inactive tablet phase, the higher the risk of a pregnancy.

Second 7 days of active tablet-taking

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

Third 7 days of active tablet-taking

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. By adhering to either of the following two options, 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 also to 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, i.e. the last small ochre active tablet on “FR”. The 7 inactive tablets must be discarded. The next pack must be started right away with the pale brown active “SA” tablet from the red section. The user is unlikely to have a withdrawal bleed until the end of the active tablets section of the second pack, but she may experience spotting or breakthrough bleeding on active tablet-taking days.
2. The woman may also be advised to discontinue active tablet-taking from the current pack. She should then have a tablet-free interval of up to 7 days, including the days she missed tablets, and subsequently

continue with the next pack, starting in the red section with the tablet for the appropriate day of the week, and use extra precautions for the next 14 days.

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

Advice in case of gastrointestinal disturbances

In the case of severe gastrointestinal disturbances, absorption may not be complete and additional contraceptive measures should be taken.

If vomiting occurs within 3 to 4 hours after active tablet-taking, the advice concerning missed tablets is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) needed from another pack.

How to delay a period

A period can be delayed for about 10 days. To delay a period the woman should complete all the small active tablets (pale brown, white and ochre) of the current pack and discard the large white inactive tablets. A new pack must then be started with the first small ochre active tablet marked “WE”. The days will not correspond to actual calendar days. One tablet must be taken daily, following the arrows on the pack. After taking the last small ochre active tablet marked “FR” from this second pack, the rest of the pack must be discarded. A third pack should then be started with the large white inactive tablet in the red section marked “TU”. The woman’s period will usually start in this section. Tablet-taking should then continue as normal. During the extension the woman may experience breakthrough-bleeding or spotting.

Special populations

Children and adolescents

LOGYNON ED is only indicated after menarche.

Geriatric patients

Not applicable. LOGYNON ED is not indicated after menopause.

Patients with hepatic impairment

LOGYNON ED is contraindicated in women with severe hepatic disease. See also section 4.3.

Patients with renal impairment

LOGYNON ED has not been specifically studied in renally impaired patients. Available data do not suggest a change in treatment in this patient population.

4.3 Contraindications

LOGYNON ED 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 LOGYNON ED use, the product should be stopped immediately.

- Presence or a history of venous or arterial thrombotic/thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction) or of a cerebrovascular accident.
- Presence or history of thrombosis (e.g. transient ischaemic attack, angina pectoris).
- Presence or risk of venous thromboembolism (VTE)
- Venous thromboembolism – current VTE (on anticoagulants) or history of (e.g. deep venous thrombosis [DVT] or pulmonary embolism [PE])
- Known hereditary or acquired predisposition for venous thromboembolism, such as APC resistance, (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency
- Major surgery with prolonged immobilisation (see section 4.4)
- A high risk of venous thromboembolism due to the presence of multiple risk factors (see section 4.4)
- Presence or risk of arterial thromboembolism (ATE)
- Arterial thromboembolism – current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infarction) or prodromal condition (e.g. angina pectoris)
- Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g. transient ischaemic attack, TIA)
- Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant)
- History of migraine with focal neurological symptoms.
- A high risk of arterial thromboembolism due to multiple risk factors (see section 4.4) or to the presence of one serious risk factor such as:
    - Diabetes mellitus with vascular involvement.
    - Severe hypertension
    - Severe dyslipoproteinaemia
- Severe hepatic disease, as long as liver function values have not returned to normal.
- Use of direct-acting antiviral (DAA) medicines containing ombitasvir, paritaprevir, or dasabuvir, and combination of these (see section 4,5).
- 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.
- Hypersensitivity to the active substances or to any of the excipients.

4.4 Special warnings and precautions for use

If any of the conditions/risk factors mentioned below are present, the benefits of LOGYNON ED 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 LOGYNON ED use should be discontinued.

Circulatory disorders

Epidemiological studies have suggested an association between the use of combined oral contraceptives and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism.

The risk of venous thromboembolism (VTE) is highest during the first year of use. This increased risk is present after initially starting a Combined Oral Contraceptives (COCs) or restarting (following a 4 week or greater pill free interval) the same or a different COC. Data from a large, prospective 3-armed cohort study suggest that this increased risk is mainly present during the first 3 months.

Overall, the risk for venous thromboembolism (VTE) in users of low estrogen dose (< 50 µg ethinylestradiol) Combined Oral Contraceptives (COCs) is two to threefold higher for non-users of COCs who are not pregnant and remains lower than the risk associated with pregnancy and delivery.

VTE may be life threatening or may have a fatal outcome (in 1 to 2 % of the cases).

Venous thromboembolism, manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of all combined oral contraceptives, including LOGYNON ED.

Thrombosis has been reported in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in combined oral contraceptive users.

Symptoms of deep venous thrombosis (DVT) can include: unilateral swelling of the leg or along a vein in the leg; pain or tenderness in the leg which may be felt only when standing or walking, increased warmth in the affected leg: red or discoloured skin on the leg.

Symptoms of pulmonary embolism (PE) can include sudden onset of unexplained shortness of breath or rapid breathing; sudden coughing which may bring up blood; sharp chest pain may increase with deep breathing; sense of anxiety; severe light headedness or dizziness; rapid or irregular heartbeat. Some of these symptoms (e.g. shortness of breath, coughing) are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infection).

An arterial thromboembolic event can include cerebrovascular accident, vascular occlusion or myocardial infarction (MI). Symptoms of a cerebrovascular accident can include: sudden numbness or weakness of the face, arm or leg, especially on one side of the body; sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden trouble walking; dizziness, loss of consciousness or fainting with or without seizure. Other signs of vascular occlusion can include sudden pain, swelling and slight blue discoloration of an extremity, acute abdomen.

Symptoms of MI can include: pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm or below the breastbone; discomfort radiating to the back, jaw, throat, arm, stomach, fullness, indigestion or choking feeling; sweating, nausea, vomiting or dizziness; extreme weakness, anxiety, or shortness of breath; rapid or irregular heartbeats.

Arterial thromboembolic events may be life-threatening or may have a fatal outcome.

The potential for an increased synergistic risk of thrombosis should be considered in women who possess a combination of risk factors or exhibit a greater severity of an individual risk factor. This increased risk may be greater than a simple cumulative risk of the factors. A combined oral contraceptive should not be prescribed in case of a negative risk benefit assessment. (see section 4.3).

The risk of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident increases with:

- age;

- obesity (body mass index over 30 kg/m^2)
- 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;
- prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations, it is advisable to discontinue combined oral contraceptive use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilization;
- smoking (with heavier smoking and increasing age the risk increases further, especially in women over 35 years of age);
- dyslipoproteinaemia;
- hypertension;
- migraine;
- valvular heart disease;
- atrial fibrillation;
- puerperium.

The increased risk of thromboembolism in the puerperium must be considered (see sections 4.3 and 4.6).

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

The onset of, or increase in frequency or severity of migraine during LOGYNON ED use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of LOGYNON ED.

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

When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with low-dose LOGYNON ED.

Tumours

A significantly increased risk of cervical cancer and breast cancer in long-term users of LOGYNON ED has been reported in epidemiological studies.

A meta-analysis from epidemiological studies reported that there is an increased relative risk of having breast cancer diagnosed in women who are currently using combined oral contraceptives.

Benign liver tumours, and rarely, malignant liver tumours have been reported in users of combined oral contraceptives. In isolated cases these tumours have led to life-threatening intra-abdominal haemorrhages. A liver tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking combined oral contraceptives.

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

Other conditions

Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using combined oral contraceptives.

Small increases in blood pressure have been reported in many women taking combined oral contraceptives, clinically relevant increases may occur. If a sustained clinically significant hypertension develops during the use of a combined oral contraceptive, then it is prudent for the physician to withdraw the combined oral contraceptive and treat the hypertension. Where considered appropriate, combined oral contraceptive use may be resumed if normotensive values can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or deteriorate with combined oral contraceptive 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.

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

Although combined oral contraceptives such as LOGYNON ED 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 combined oral contraceptives including LOGYNON ED (containing < 0,05 mg ethinylestradiol). However, diabetic women should be carefully observed while taking LOGYNON ED.

Crohn's disease and ulcerative colitis have been associated with combined oral contraceptive 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 combined oral contraceptives.

Respiratory: Asthma may deteriorate in women using LOGYNON ED.

In women with hereditary angioedema, LOGYNON ED may induce or exacerbate symptoms of angioedema.

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

Contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption who are on lactose-free diet should take this amount into consideration.

Medical examination/consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of combined oral contraceptive use, guided by the sections 4.3 and 4.4, and should be repeated periodically. Periodic medical assessment is also of importance because contraindications (e.g. a transient ischaemic

attack, etc) or risk factors (e.g. a family history of venous or arterial thrombosis) may appear for the first time during the use of a combined oral contraceptive. The frequency and nature of these assessments should be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests.

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

Reduced efficacy

The efficacy of combined oral contraceptives may be reduced in the event of e.g. missed active tablets, gastrointestinal disturbances during active tablet-taking (see section 4.2), or concomitant medication (see section 4.5).

Reduced cycle control

With all combined oral contraceptives such as LOGYNON ED, 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 LOGYNON ED has been taken according to the directions described in "Dosage and directions for use", it is unlikely that the woman is pregnant. However, if the combined oral contraceptive 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 LOGYNON ED is continued.

4.5 Interaction with other medicines and other forms on interaction

Interactions can occur with drugs that induce microsomal enzymes, which can result in increased clearance of sex hormones and may lead to breakthrough bleeding and/or contraceptive failure.

Effects of other medicines on LOGYNON ED

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 drug therapy enzyme induction may be sustained for about 4 weeks.

Women on treatment with any of these medicines should temporarily use a barrier method in addition to the combined oral contraceptive or choose another method of contraception. The barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation. If the period during which the barrier method is used runs beyond the end of the hormone-containing ochre coated tablets in the LOGYNON ED pack, the hormone-free tablets larger white coated tablets should be omitted, and the next combined oral contraceptive pack should be started.

Substances decreasing the clearance of combined oral contraceptives (enzymes inhibitors)

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice 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 oral contraceptive containing 0,035 mg Ethinylestradiol.

Substances increasing the clearance of combined oral contraceptives (diminished efficacy of combined oral contraceptives by enzyme-induction, e.g.
phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin, products containing St John's Wort.

Substances with variable effects on the clearance combined oral contraceptives, e.g.
When co-administered with combined oral contraceptives, 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 of LOGYNON ED on other medicines

LOGYNON ED may interfere with the metabolism of other medicines. Accordingly, plasma and tissue concentrations may either increase (e.g. an increase in ciclosporin and benzodiazepines) or decrease (e.g. lamotrigine). **Plasma concentrations of lamotrigine are decreased by 50 %.**

In vitro, Ethinylestradiol is a reversible inhibitor of CYP2C19, CYP1A1 AND CYP1A2 as well as a mechanism-based inhibitor of CYP3A4/5, CYP2C8, and CYP2J2. In clinical studies, administration of a hormonal contraceptive containing Ethinylestradiol did not lead to any increase or only to a weak increase in plasma concentration of CYP3A4 substrate (e.g. midazolam) while plasma concentration of CYP1A2 substrates can increase weakly (e.g. theophylline) or moderately (e.g. melatonin and tizanidine)

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

Pharmacodynamic interactions

Co-administration of ethinylestradiol-containing medicines with direct-acting antiviral (DAA) medicines containing ombitasvir, paritaprevir, or dasabuvir, and combinations of these has been shown to be associated with increase in alanine aminotransferase (ALT) levels to greater than 20 times the upper limit of normal in healthy female subjects and hepatitis C virus (HCV) infected women (see section 4.3).

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.

4.6 Pregnancy and lactation

Pregnancy
LOGYNON ED is contraindicated during pregnancy. If pregnancy occurs during treatment with LOGYNON ED, further intake must be stopped (see section 4.3).

Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used combined oral contraceptives prior to pregnancy, nor a teratogenic effect when combined oral contraceptives were taken inadvertently during early pregnancy.

Lactation
Lactation may be influenced by combined oral contraceptives as they may reduce the quantity and change the composition of breast milk. Therefore, the use of combined oral contraceptives should generally not be recommended until the nursing mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk.

4.7 Effects on ability to drive and use machine

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 combined oral contraceptives.

4.8 Undesirable effects

a) Summary of the safety profile

The most commonly reported adverse reactions with LOGYNON ED are nausea, abdominal pain, increased weight, headache, depressed mood, altered mood, breast pain, breast tenderness. They occur in ≥ 1 % of users.

Serious adverse reactions are arterial and venous thromboembolism,

b) Tabulated summary of adverse reactions

Side effects that have been reported in users of LOGYNON ED but for which the association has been neither confirmed nor refuted are:

System organ class	Common (≥ 1/100)	Uncommon (≥ 1/1000 and < 1/100)	Rare (< 1/1000)
Eye disorders			Contact lens intolerance
Gastrointestinal disorders	Nausea Abdominal pain	Vomiting Diarrhoea	
Immune system disorders			Hypersensitivity
Investigations	Weight increased		Weight decreased
Metabolism and nutrition disorders		Fluid retention	
Nervous system disorders	Headache	Migraine	
Psychiatric disorders	Depressed mood Mood altered	Libido decreased	Libido increased
Reproductive system and breast disorders	Breast pain Breast tenderness	Breast hypertrophy	Vaginal discharge Breast discharge

Skin and subcutaneous tissue disorders		Rash Urticaria	Erythema nodosum Erythema multiforme
Vascular disorders			Venous and arterial thromboembolic events**

**- Estimated frequency, from epidemiological studies encompassing a group of combined oral contraceptives
- 'Venous and arterial thromboembolic events' summarizes the following Medical Entities: Peripheral deep venous occlusion, thrombosis and embolism/Pulmonary vascular occlusion, thrombosis, embolism and infarction/Myocardial infarction/Cerebral infarction and stroke not specified as haemorrhagic

c) Description of selected adverse reactions

Adverse reactions with very low frequency or with delayed onset of symptoms which are considered to be related to the group of combined oral contraceptives are listed below (see also sections 4.3 and 4.4).

Tumours

- The frequency of diagnosis of breast cancer is very slightly increased among oral contraceptive 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. Causation with combine oral contraceptive use is unknown.
- Liver tumours (benign and malignant)

Other conditions

- Women with hypertriglyceridemia (increased risk of pancreatitis when using combined oral contraceptives)
- Hypertension
- Occurrence or deterioration of conditions for which association with COC use is not conclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss
- In women with hereditary angioedema exogenous estrogen may induce or exacerbate symptoms of angioedema
- Liver function disturbances
- Chane in glucose tolerance or effect on peripheral insulin resistance
- Crohn's disease, ulcerative colitis
- Chloasma

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form"** ,found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 .

4.9 Overdose

There have been no reports of serious deleterious effects from overdose. Symptoms that may occur in case of taking an overdose of hormone-containing tablets are nausea; vomiting; and withdrawal bleeding. The last may even occur in girls before their menarche, if they have accidentally taken the medicines. There are no antidotes and further treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 21.8.2 Progesterones with estrogens
Pharmacotherapeutic group: Progesterone and estrogen, fixed combination
ATC Code: G03AA

This medicine is a low dose triphasic oral contraceptive with estrogenic and progestogenic peripheral effects.

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.

Post Authorization Safety Studies (PASS) have shown that the frequency of VTE diagnosis range between 7 to 10 per 10 000-woman years in low estrogen dose (< 50 µg ethinylestradiol) COC users. The most recent data suggest that the frequency of VTE diagnosis is approximately 4 per 10 000-woman years in non-pregnant non-combined oral contraceptive users and ranges between 20 to 30 per 10 000 pregnant women or postpartum.

5.2 Pharmacokinetic properties

- **Levonorgestrel**

Absorption
Orally administered levonorgestrel is rapidly and completely absorbed. Maximum levonorgestrel concentrations in serum of 2,3 ng/ml are reached about 1 hour after start of treatment with LOGYNON ED. Following single ingestion of 0,125 mg levonorgestrel together with 0,03 mg ethinylestradiol (which represents the combination with the highest levonorgestrel content of the triphasic formulation), peak serum concentrations of 4,3 ng/ml are reached at about 1 hour after single ingestion. Levonorgestrel is almost completely bioavailable after oral administration.

Distribution
Levonorgestrel is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 1,4 % of the total serum drug concentrations are present as free steroid, 55 % are specifically bound to SHBG and about 44 % are non-specifically bound to albumin. The ethinylestradiol-induced increase in SHBG influences the proportion of levonorgestrel bound to the serum proteins, causing an increase of the SHBG-bound fraction and a decrease of the albumin-bound fraction. The apparent volume of distribution of levonorgestrel is about 128 l after single oral administration of the highest levonorgestrel dose of LOGYNON ED.

Metabolism

Levonorgestrel is extensively metabolized. The major metabolite in plasma are the unconjugated and conjugated forms of 3α, 5β-tetrahydrolevonorgestrel. Based on *in vivo* and *in vitro* studies, CYP3A4 is the main enzyme involved in the metabolism of levonorgestrel. The clearance rate from serum is approximately 1,0 ml/min/kg after single oral administration of the highest levonorgestrel dose of LOGYNON ED.

Elimination
Levonorgestrel serum levels decrease in two phases. The terminal disposition phase is characterised by a half-life of approximately 22 hours. Levonorgestrel is not excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of about 1:1. The half-life of metabolite excretion is about 1 day.

Steady state conditions
Levonorgestrel pharmacokinetics are influenced by SHBG levels, which are increased about twofold during the 21-day treatment period with LOGYNON ED. Following daily ingestion, drug serum levels increase about fourfold, reaching steady-state conditions during the second half of a treatment cycle. At steady state, the volume of distribution and the clearance rate are reduced to 52 l and 0,5 ml/min/kg, respectively.

- **Ethinylestradiol**

Absorption
Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of about 116 pg/ml are reached within 1,3 hours. During absorption and first liver passage, ethinylestradiol is metabolised extensively, resulting in a mean oral bioavailability of about 45 % with a large interindividual variation of about 20 to 65 %.

Distribution
Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98 %) and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 2,8 to 8,6 l/kg was reported.

Metabolism
Ethinylestradiol is subject to pre-systemic conjugation in both the small bowel mucosa and the liver. Ethinylestradiol is primarily metabolised by aromatic hydroxylation, but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulphate. The clearance rate was reported to be 2,3 to 7 ml/min/kg.

Elimination
Ethinylestradiol serum levels decrease in two disposition phases characterised by half-lives of about 1 hour and 10 to 20 hours, respectively. Unchanged drug is not excreted; ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 1 day.

Steady-state conditions
According to the variable half-life of the terminal disposition phase from serum and the daily ingestion, steady-state serum levels of ethinylestradiol will be reached after about one week. At the end of treatment, the maximum ethinylestradiol concentration of about 132 pg/ml is reached after about 1,3 hours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

calcium carbonate
ferric oxide pigment red
ferric oxide pigment yellow
glycerol 85 %
lactose monohydrate
magnesium stearate
maize starch
montan glycol wax
macrogol 6 000
povidone 25 000
povidone 700 000
sucrose
talc
titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

In original packs at room temperature (at or below 25 °C). Protect from light.
KEEP OUT OF REACH OF CHILDREN.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and content of container

Cartons with one or three blister calendar packs containing 28 tablets.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Bayer (Pty) Ltd
Reg. No.: 1968/011192/07
27 Wrench Road
ISANDO
1609

8 REGISTRATION NUMBER(S)

N/21.8.2/113

9 DATE OF FIRST AUTHORISATION

02 April 1981

10 DATE OF REVISION OF THE TEXT

17 March 2022