DATA SHEET

1. LEVLEN® ED

Levlen ED 30 micrograms ethinylestradiol and 150 micrograms levonorgestrel tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One active tablet contains 30 micrograms ethinylestradiol and 150 micrograms levonorgestrel. Each blister pack contains 21 active tablets and 7 hormone-free tablets.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sugar-coated tablets

The active tablets are beige, biconvex, round and 5.7mm in diameter. The hormone-free tablets are white, biconvex, round and 6.8mm in diameter.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Oral contraception.

4.2. Dose and method of administration

Combined oral contraceptives (COCs), such as Levlen ED, 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 Levlen ED

Tablets must be taken in the order directed on the package every day at about the same time with some water as needed. Tablet-taking is continuous following the directional arrows. One tablet is to be taken daily for 28 consecutive days. Each subsequent pack is started the day after the last tablet of the previous pack. Withdrawal bleeding usually starts on day 2 - 3 after starting the white hormone-free tablets and may not have finished before the next pack is started.

How to Start Levlen ED

START WITH THE FIRST TABLET FROM THE GREEN SECTION MARKED WITH THAT DAY OF THE WEEK, in accordance with one of the following:

<u>No preceding hormonal contraceptive use (in the past month)</u>

Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). Starting on days 2 - 5 of the menstrual cycle is allowed, but

during the first cycle an additional barrier contraceptive method is recommended for the first 7 days of tablet-taking.

Changing from another combined oral contraceptive (COC), vaginal ring or transdermal patch

The woman should start with Levlen ED preferably on the day after the last active tablet of her previous COC, but at the latest on the day following the usual tablet-free or hormone-free tablet interval of her previous COC.

In case a vaginal ring or transdermal patch has been used, the woman should start taking Levlen ED preferably on the day of removal of the ring or patch, but at the latest when the next application would have been due.

Changing from a progestogen-only method (minipill, injection, implant) or progestogen-releasing intrauterine system (IUS)

The woman may switch any day from the minipill, or from an implant or IUS on the day of its removal, or from an injectable when the next injection would be due. In all of these cases, the woman should be advised to additionally use a barrier contraceptive method for the first 7 days of tablet-taking.

Following first-trimester abortion

The woman may start tablet-taking immediately. When doing so, she does not need additional contraceptive measures.

Following delivery or second-trimester abortion

The woman should be advised to start on day 21 to 28 after delivery or second-trimester abortion. When starting later than this, the woman should be advised to additionally use a barrier contraceptive method for the first 7 days of tablet-taking.

However, if intercourse has already occurred, pregnancy should be excluded before starting Levlen ED or the woman has to wait for her first menstrual period.

For breastfeeding women, see section 4.6.

Management of Missed Tablets

Errors in taking the white hormone-free tablets contained in Levlen ED can be ignored. However, they should be discarded to avoid unintentionally prolonging the hormone-free tablet phase. The following advice only refers to missed beige active tablets:

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

If the woman is **more than 12 hours** late in taking any beige active tablet, contraceptive protection may be reduced.

There is a particularly high risk of pregnancy if tablets are missed just before or immediately after taking the white hormone-free tablets. If tablets are missed in the first week of taking the beige active tablets following the white hormone-free tablets and intercourse took place in the preceding 7 days, the possibility of pregnancy should be considered.

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

These rules form the basis of the instructions to patients provided in the package insert.

Extra Contraceptive Precautions

When you need extra contraceptive precautions, either:

- don't have sex; or
- use a cap plus spermicide; or
- use a condom

Do not use the rhythm or temperature methods as extra contraceptive precautions. This is because oral contraceptives alter the usual menstrual cycle changes, such as changes in temperature and cervical mucus.

The 7 Day Rule

- Continue taking your Pills.
- You will not be protected from pregnancy until you have taken your daily beige active Pill for the next 7 days in a row.
- Use another method of contraception (see "*Extra Contraceptive Precautions"*) such as condoms or do not have sexual intercourse for these next 7 days.
- If there are fewer than 7 beige active Pills left in the pack, or before the white placebo Pills in the pack, go straight on to the active Pills in the green section of the next pack. This means that you miss out the white placebo Pills. You may not have a period until the end of the next pack. This is not harmful.

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

Advice in Case of Gastrointestinal Disturbances

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

If vomiting or severe diarrhoea occurs within 3 - 4 hours after taking the beige active tablet, 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 Shift Periods or How to Delay a Period

To delay a period the woman should continue with the beige active tablets from another pack of Levlen ED without taking the white hormone-free tablets from her current pack. The extension can be carried on for as long as desired until the end of the beige active tablets in the second pack. During the extension the woman may experience breakthrough bleeding or spotting. Regular intake of Levlen ED is then resumed after the usual 7-day hormone-free tablet phase.

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 hormone-free tablet phase by as many days as she likes. The shorter the hormone-free interval, the

higher the risk that she does not have a withdrawal bleed and will experience breakthrough-bleeding and spotting during the second pack (just as when delaying a period).

4.3. Contraindications

Combined oral contraceptives 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 their use, the product should be stopped immediately.

- Presence or risk of venous thromboembolism (VTE) (see 4.4 Special warnings and precautions for use)
  - Current VTE (on anticoagulants) or history of 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
  - A high risk of VTE due to the presence of multiple risk factors
- Presence or risk of arterial thromboembolism (ATE) (see 4.4 Special warnings and precautions for use)
  - Current ATE or history of ATE (e.g. myocardial infarction or stroke) or prodromal condition (e.g. angina pectoris or transient ischaemic attack [TIA])
  - Known hereditary or acquired predisposition for ATE, such as hyperhomocysteinaemia and antiphospholipid-antibodies (e.g. anticardiolipin- antibodies and lupus anticoagulant)
  - History of migraine with focal neurological symptoms
  - A high risk of ATE due to multiple risk factors or to the presence of one serious risk factor such as:
    - diabetes mellitus with vascular symptoms
    - severe hypertension
    - severe dyslipoproteinaemia
- Severe hepatic disease as long as liver function values have not returned to normal
- Use of direct-acting antiviral (DAA) medicinal products containing ombitasvir, paritaprevir, or dasabuvir, and combinations 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 any of the ingredients in Levlen ED.

4.4. Special warnings and precautions for use

The clinical and epidemiological evidence for COCs like Levlen ED is predominantly based on experience with COCs in general. Therefore, the following warnings related to the use of COCs apply also to the use of Levlen ED.

If any of the conditions/risk factors mentioned below are present, the benefits of Levlen ED should be weighed against the possible risks for each individual woman

and discussed with the woman before she decides to start taking it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her doctor. The doctor should then decide whether Levlen ED should be discontinued.

Circulatory Disorders

Epidemiological studies have suggested an association between the use of COCs containing ethinyloestradiol and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism. These events occur rarely in average-risk women.

Risk of venous thromboembolism (VTE)

The use of any COC increases the risk of VTE compared with no use. The woman should be advised that her VTE risk is highest in the first ever year of use and that there is some evidence that the risk is increased when a COC is re-started after a break in use of 4 weeks or more.

Data from a large, prospective 3-arm cohort study suggest that this increased risk is mainly present during the first 3 months.

Post Authorisation Safety Studies (PASS) have shown that the frequency of VTE diagnosis ranges from 7-10 per 10,000 woman-years in low-oestrogen-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-COC users and ranges from 20 to 30 per 10,000 woman-years in pregnant women or in the post-partum period.

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

It is important that women understand that VTE associated with COC use is rare in average-risk women. The risk in pregnancy (5-20 per 10,000 women over 9 months) and the risk in the post-partum period (45-65 per 10,000 women over 12 weeks) is higher than that associated with COC use.

An additional increase in VTE risk for COCs containing ≥ 50 µg ethinyloestradiol cannot be excluded.

The decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with COCs, and how her current risk factors influence this risk.

The increased risk of VTE during the postpartum period must be considered if re-starting Levlen ED (see 4.2 Dose and method of administration and 4.6 Fertility, pregnancy and lactation).

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

Extremely rarely, thrombosis has been reported to occur in COC users in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries.

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 list below).

Levlen ED is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis. 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.

When considering risk/benefit, the doctor should take into account that the adequate treatment of a condition may reduce the associated risk of thrombosis.

Risk factors for VTE

- Obesity (body mass index over 30 kg/m²). Risk increases substantially as BMI rises
- Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma
- Temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors
- Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50)
- Biochemical factors that may be indicative of hereditary or acquired predisposition for VTE include Activated Protein C (APC) resistance (including Factor V Leiden), antithrombin-III deficiency, protein C deficiency, protein S deficiency
- Other medical conditions associated with VTE include
  - Cancer
  - Systemic lupus erythematosus
  - Haemolytic uraemic syndrome
  - Chronic inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis)
  - Sickle cell disease.
- Increasing age, particularly above 35 years
- Smoking

In women at risk of prolonged immobilisation (including major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma), it is advisable to discontinue use of Levlen ED (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 Levlen ED has not been discontinued in advance.

If a hereditary predisposition to VTE is suspected, the woman should be referred to a specialist for advice before deciding about any COC use.

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

Symptoms of VTE (DVT and PE)

Women should be informed of the symptoms of VTE and be advised to seek urgent medical attention if VTE symptoms develop and to inform the healthcare professional that she is taking a COC.

Symptoms of 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 PE can include:

- sudden onset of unexplained shortness of breath or rapid breathing

- sudden coughing which may be associated with haemoptysis
- sharp chest pain or sudden severe pain in the chest which may increase with deep breathing
- 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 discoloration 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)

Epidemiological studies have associated the use of COCs with an increased risk for ATE (e.g. myocardial infarction, angina pectoris, stroke or TIA). Arterial thromboembolic events may be fatal.

The risk of arterial thromboembolic complications in COC users increases in women with risk factors. Levlen ED is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis. 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 a COC should not be prescribed.

<u>Risk factors for ATE</u>

- Increasing age, particularly above 35 years
- Smoking
- Hypertension
- Obesity
- Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g. below 50)
- Biochemical factors that may be indicative of hereditary or acquired predisposition for ATE include: hyperhomocysteinaemia and antiphospholipid antibodies (e.g. anticardiolipin antibodies, and lupus anticoagulant)
- Migraine
- Other medical conditions associated with adverse vascular events:
  - Diabetes mellitus
  - Hyperhomocysteinaemia
  - Valvular heart disease
  - Atrial fibrillation
  - Dyslipoproteinaemia
  - Systemic lupus erythematosus

Women should be advised not to smoke if they wish to use a COC. Women over 35 years who continue to smoke should be strongly advised to use a different method of contraception.

If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use.

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.

Symptoms of ATE

Women should be informed of the symptoms of ATE and be advised to seek urgent medical attention if ATE symptoms develop and to inform the healthcare professional that she is taking a COC.

Symptoms of a stroke 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, slurred speech or aphasia
- sudden partial or complete loss of vision; diplopia
- 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 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

Tumours

The most important risk factor for cervical cancer is persistent human papilloma virus (HPV) infection. Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, e.g. cervical screening and sexual behaviour including use of barrier contraceptives.

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently taking COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

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 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 COCs.

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 taking COCs.

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. However, if a sustained clinically significant hypertension develops during the use of a COC, then it is prudent for the doctor to withdraw the COC and treat the hypertension. 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; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic 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 or kidney function may necessitate the discontinuation of COC use until markers of liver or kidney function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or 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 women with diabetes taking low-dose COCs (containing < 0.05 mg ethinylestradiol). However, women with diabetes should be carefully observed while taking COCs.

Crohn's disease and ulcerative colitis have been associated with 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 beige active tablet contains 32.97 mg of lactose and each white hormone-free tablet contains 48.25 mg of lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption who are on a 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 Levlen ED, guided by sections 4.3 and 4.4. This should be repeated at least annually during the use of Levlen ED. Periodic medical assessment is also of importance because contraindications (e.g. a transient ischemic 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 COC. The frequency and nature of these assessments should be based on established practice guidelines and 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.

Sexually Transmitted Infections (STIs) including Human Immunodeficiency Virus (HIV) infections and Acquired Immune Deficiency Syndrome (AIDS)

Women should be advised that oral contraceptives like Levlen ED do not protect against HIV infections (AIDS) and other sexually transmissible infections (STIs). The

woman should be advised that additional barrier contraceptive measures are needed to prevent transmission of STIs.

Reduced Efficacy

The efficacy of Levlen ED may be reduced in the event of missed beige active tablets (see section 4.2 - *Management of Missed Tablets*), vomiting or severe diarrhoea (see section 4.2 - *Advice in Case of Gastrointestinal Disturbances)* or concomitant medication (see section 4.5).

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 while taking the 7 white hormone-free tablets. If the COC has been taken according to the directions described section 4.2, 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.

Use in Children

Levlen ED is only indicated after menarche.

Use in the Elderly

Levlen ED is not indicated after menopause.

Patients with Hepatic Impairment

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

Patients with Renal Impairment

Levlen ED has not been specifically studied in renally impaired patients. There is no data suggesting the need for a dosage adjustment in patients with renal impairment.

4.5. Interaction with other medicines and other forms of interaction

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

Effects of Other Medicines on Levlen ED

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

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 COC or choose another method of contraception. The barrier method should be used during the time of concomitant medicine administration and for 28 days after its discontinuation. If the period during which the barrier method is used runs beyond the end of the beige active tablets in the Levlen ED pack, the white hormone-free tablets should be omitted and the next Levlen ED pack should be started.

Substances increasing the clearance of COCs (diminished efficacy of COCs by enzyme-induction), e.g.:

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

Substances with variable effects on the clearance of COCs:

When co-administered with COCs, many human immunodeficiency virus (HIV)/hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of estrogen or progestogen. These changes may be clinically relevant in some cases.

Substances decreasing the clearance of COCs (enzyme 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 hormonal contraceptive containing 0.035 mg ethinylestradiol.

Influence of Levlen ED on other Medicines

Oral contraceptives such as Levlen ED may interfere with the metabolism of other medicines. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporin) or decrease (e.g. lamotrigine).

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 lead to no, or a weak increase in CYP3A4 substrates (e.g. midazolam) and a weak (e.g. theophylline) to moderate (e.g. melatonin, tizanidine) increase of CYP1A2 substrates.

Pharmacodynamic Interactions

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

Laboratory Tests

The use of preparations like Levlen ED 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. Fertility, pregnancy and lactation

Use in Pregnancy (Category B3)

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

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 inadvertently during early pregnancy.

Use in Lactation

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

4.7. Effects on ability to drive and use machines

No studies on 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.

4.8. Undesirable effects

Serious undesirable effects of Levlen ED have been referred to in sections 4.3 and 4.4.

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

Serious adverse reactions are arterial and venous thromboembolism.

In addition, the following undesirable effects have been reported in users of COCs such as Levlen ED, although the causal relationships have not been confirmed:

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	Increased weight		Decreased weight
Metabolism and		Fluid retention	

System Organ Class	Common (≥ 1/100)	Uncommon (≥ 1/1000 and < 1/100)	Rare (< 1/1000)
Nutrition Disorders			
Nervous System Disorders	Headache	Migraine	
Psychiatric Disorders	Depressed mood, altered mood	Decreased libido	Increased libido
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.

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

4.9. Overdose

There have been no reports of serious deleterious effects from overdose.

Symptoms

Symptoms that may occur in case of taking an overdose of beige active tablets are: nausea, vomiting and withdrawal bleeding. The last may even occur in girls before their menarche, if they have accidentally taken the medicinal product.

Treatment

There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

The contraceptive effect of Levlen ED 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. When Levlen ED is taken according to instructions, the egg cells are prevented from maturing to the point at which they can be fertilised, the cervical mucus remains thick so as to constitute a barrier to sperm, and the endometrium is rendered unreceptive to implantation.

As well as protection against pregnancy, combined oral contraceptives (COCs) have several positive properties which, next to the negative properties (see sections 4.4 and 4.8), can be useful in deciding on the method of birth control.

With COCs the cycle is more regular and menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency. Apart from this there is evidence of a reduced risk of endometrial cancer and ovarian cancer. Furthermore, for the higher-dosed COCs containing 0.05 mg ethinylestradiol, there is evidence of a reduced risk of ovarian cysts, pelvic inflammatory disease, benign breast disease and ectopic pregnancy. Whether this also applies to lower-dosed COCs remains to be confirmed.

5.2. Pharmacokinetic properties

Ethinylestradiol

Absorption

Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of approximately 95 pg/mL are reached within 1 - 2 hours. During absorption and first-pass liver passage, ethinylestradiol is metabolised extensively, resulting in a mean oral bioavailability of approximately 45% with a large interindividual variation of approximately 20 - 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 approximately 2.8 - 8.6 L/kg was reported.

Metabolism

Ethinylestradiol is subject to presystemic conjugation in both 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 sulfate. The metabolic clearance rate was reported to be 2.3 - 7 mL/min/kg.

Elimination

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

Steady-State Conditions

Ethinylestradiol serum concentrations increase slightly after daily oral administration of Levlen ED. The maximum concentrations are approximately 114 pg/mL at the end of a treatment cycle.

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 approximately one week.

Levonorgestrel

Absorption

Orally administered levonorgestrel is rapidly and completely absorbed. Peak serum concentrations of 3 - 4 ng/mL are reached 1 hour after single ingestion.

Levonorgestrel is almost completely bioavailable after oral administration.

Distribution

Levonorgestrel is bound to serum albumin and sex hormone binding globulin (SHBG). Only around 1.3% of the total serum medicine concentrations are present as free steroid, approximately 64% are specifically bound to SHBG and about 35% 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 184 L after single administration.

Metabolism

Levonorgestrel is extensively metabolised. The major metabolites in plasma are the unconjugated and conjugated forms of 3α, 5β-tetrahydrolevonorgestrel. Additionally, based on *in vitro* and *in vivo* studies, CYP3A4 is the main enzyme involved in the oxidative metabolism of levonorgestrel.

The metabolic clearance rate from serum is approximately 1.3 - 1.6 mL/min/kg.

Elimination

Levonorgestrel serum levels decrease in two phases. The terminal disposition phase is characterised by a half-life of approximately 20 - 23 hours. Levonorgestrel is not excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of approximately 1:1. The half-life of metabolite excretion is approximately 1 day.

Steady-state conditions

Following daily ingestion, medicine serum levels increase approximately three- to four-fold reaching steady-state conditions during the second half of the treatment cycle.

Levonorgestrel pharmacokinetics are influenced by SHBG levels, which are increased approximately 1.7 fold after daily oral administration of Levlen ED. This effect leads to a reduction of the clearance rate to about 0.7 mL/min/kg at steady state.

5.3. Preclinical safety data

Preclinical data reveal no special risks for humans based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. However, it should be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Calcium carbonate, glycerol, glycol montanate, iron oxide yellow, lactose monohydrate, macrogol 6000, magnesium stearate, maize starch, povidone, purified talc, sucrose, titanium dioxide.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

5 years

6.4. Special precautions for storage

Store below 25ºC.

6.5. Nature and contents of container

PVC/Aluminium blisters. Pack sizes of 1 x 28 or 3 x 28 tablets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Bayer New Zealand Limited
3 Argus Place
Hillcrest
North Shore
AUCKLAND 0627

Free Phone: 0800 233 988

9. DATE OF FIRST APPROVAL

08 September 1997

10. DATE OF REVISION OF THE TEXT

24 April 2018

Summary table of changes

Section changed	Summary of new information
4.3 Contraindications	Updates regarding VTE and ATE
4.4 Special warnings and precautions for use	Updates regarding the risk of VTE and ATE, including explanation about the risk factors and symptoms of VTE and ATE.

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