AUSTRALIAN PRODUCT INFORMATION

LENEST 20 ED

(Levonorgestrel/ethinylestradiol) tablets

1 NAME OF THE MEDICINE

Levonorgestrel/ethinylestradiol

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pink active tablet contains levonorgestrel 100 μg and ethinylestradiol 20 μg as the active ingredients.

Excipients of known effect: lactose (present in both pink active tablet and green placebo tablet).

For the full list of excipients see section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

LENEST 20 ED is a combined oral contraceptive (COC) tablet containing the synthetic progestogen levonorgestrel and the synthetic estrogen ethinylestradiol.

The active tablets are round, pink, uncoated flat tablets debossed '405' on one side and the other side is plain.

The placebo tablets are round, green, uncoated flat tablets debossed '471' on one side and the other side is plain.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

LENEST 20 ED is indicated for the prevention of pregnancy.

4.2 DOSE AND METHOD OF ADMINISTRATION

How to Take LENEST 20 ED

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

One tablet is to be taken daily. The tablets must be taken in the order directed on the package at about the same time each day, with some liquid as needed. Daily tablet taking should be continuous for 28 consecutive days, starting with a pink active tablet marked with the corresponding day of the week from the green area of the LENEST 20 ED pack. Each subsequent pack is to be started the day after the last tablet of the previous pack. A withdrawal bleed usually starts on day 2 to 3 after starting the green placebo tablets (last row) and may not have finished before the next pack is started.

How to Start LENEST 20 ED

No Preceding Hormonal Contraceptive Use (in the past month)

Tablet-taking must start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). If started on day 1 in this way, protection against pregnancy is immediate and no additional method of contraception is required. Starting on day 2-5 of the menstrual cycle is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of tablet-taking.

When Changing Pills

Changing From a Combined Hormonal Contraceptive or Vaginal Ring

The woman should start with LENEST 20 ED preferably on the day after her last active tablet (the last tablet containing the active substances) of her previous COC, but at the latest on the day following the usual tablet free or placebo tablet interval of her previous COC.

In case a vaginal ring has been used, the woman should start taking LENEST 20 ED preferably on the day of removal, but at the latest when the next application would have been due.

Changing From a Progestogen Only Method (minipill, injection, implant) or From a Progestogen-releasing Intrauterine System (IUS)

The woman may switch any day from the minipill, an implant, IUS on the day of its removal or from an injectable when the next injection would be due, but in all of these cases should be advised to additionally use a barrier 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

Women should be advised to start on day 21 to 28 after delivery or second trimester abortion. When starting later than day 28, the woman should be advised to additionally use a barrier method for the first 7 days of tablet taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

For breastfeeding women see section 4.6 Fertility, Pregnancy and Lactation - Use in Lactation.

Additional Contraceptive Precautions

When additional contraceptive precautions are required, the woman should be advised either to abstain from sex, or to use a barrier method of contraception, such as a cap (or diaphragm) plus spermicide, or for her partner to use a condom. Rhythm methods should not be advised as the combined oral contraceptive disrupts the cyclical changes associated with the natural menstrual cycle, e.g. changes in temperature and cervical mucus.

How to Shift Periods or How to Delay a Period

To delay a period the woman should continue with another pack of LENEST 20 ED by missing the green placebo tablets (last row) from her current pack. The extension can be carried on for as long as wished until the end of the second pack. During the extension the woman may experience breakthrough-bleeding or spotting. Regular intake of LENEST 20 ED is then resumed after the usual 7-day placebo tablet 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 placebo tablet 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 the second pack (just as when delaying a period).

How to Manage Reduced Reliability

When LENEST 20 ED is taken according to the directions for use, the occurrence of pregnancy is highly unlikely. However, the reliability of combined oral contraceptives may be reduced under the following circumstances:

Management of Missed Tablets

Missed pills from the last row of the blister are placebo tablets and thus can be disregarded. However, they should be discarded to avoid unintentionally prolonging the placebo tablet phase. *The following advice only refers to missed pink active tablets (rows 1-3 of the blister):*

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

If the woman is **more than 12 hours late** in taking any pink active tablet, contraceptive protection may be reduced. The more pink active tablets missed and the closer they are to the green placebo tablet phase the higher the risk of a pregnancy.

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

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

Week 1 of Active Tablets

The woman should take the last missed pink active tablet as soon as she remembers, even if this means taking two pink active 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.

Week 2 of Active Tablets

The woman should take the last missed pink active tablet as soon as she remembers, even if this means taking two pink active 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 pink active tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than one pink active tablet, the woman should be advised to use extra precautions for 7 days.

Week 3 of Active Tablets

The risk of reduced reliability is imminent because of the forthcoming green placebo 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 pink active 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 to use extra precautions for the next 7 days as well:

1. The woman should take the last missed pink active tablet as soon as she remembers, even if this means taking two pink active tablets at the same time. She then continues to take tablets at her usual time until all the pink active tablets are taken. The 7 green placebo tablets from the last row must be discarded. The next pack must be started right away. The woman is unlikely to have a withdrawal bleed until the end of the active tablets 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 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

If the woman missed tablets and subsequently has no withdrawal bleed in the hormone-free green 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 occurs within 3 to 4 hours after tablet-taking the advice concerning missed tablets, as given previously, 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.

4.3 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.

- Presence or risk of venous thromboembolism (VTE) (see section 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 venous thromboembolism due to the presence of multiple risk factors
- Presence or risk of arterial thromboembolism (ATE) (see section 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 arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (e.g. anticardiolipin antibodies and lupus anticoagulant)
    - History of migraine with focal neurological symptoms
    - A high risk of arterial thromboembolism 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
- Pancreatitis or a history thereof if associated with severe hypertriglyceridaemia
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- LENEST 20 ED is contraindicated for concomitant use with the medicinal products glecaprevir, pibrentasvir, sofosbuvir, velpatasvir, voxilaprevir, ombitasvir, paritaprevir, or dasabuvir, and

combinations of these (see section 4.4 Special Warnings and Precautions for Use and 4.5 Interactions with Other Medicines and Other Forms of Interactions)

- 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 LENEST 20 ED

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

If any of the conditions/risk factors mentioned below are present, the benefits of combined oral contraceptive use 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 on whether COC use should be discontinued.

Circulatory Disorders

Epidemiological studies have suggested an association between the use of combined oral contraceptives containing ethinylestradiol 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 combined hormonal contraceptive (CHC) 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 CHC is re-started after a break in use of 4 weeks or more.

Data from a large, prospective 3-armed cohort study (EURAS[1] and LASS[2]) suggest that this increased risk is mainly present during the first 3 months.

A large prospective 3-armed cohort study has shown that the frequency of VTE diagnosis range from 8 to 10 per 10,000 woman years in low estrogen dose (< 50 μg ethinylestradiol) COC users. The most recent data suggests that the frequency of VTE diagnosis is approximately 4.4 per 10,000 woman years in non-pregnant non-COC users and ranges from 20 to 30 per 10,000 in pregnancy or the post-partum period.

Overall the risk of VTE in users of low estrogen dose (< 50 μg ethinylestradiol) COCs is two to three-fold 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 CHC 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 CHC use.

An additional increase in VTE risk for CHCs containing ≥ 50 μg ethinylestradiol 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 CHCs, and how her current risk factors influence this risk.

The increased risk of VTE during the postpartum period must be considered if re-starting LENEST 20 ED. See section 4.2 Dose and Method of Administration and section 4.6 Fertility, Pregnancy and Lactation – Use in Pregnancy; Use in 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 CHC users in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries.

The risk for venous thromboembolic complications in CHC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see list below).

LENEST 20 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 CHC 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 LENEST 20 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 LENEST 20 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 CHC use.

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

Symptoms of VTE (deep vein thrombosis and pulmonary embolism)

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 CHC.

Symptoms of deep vein thrombosis (DVT) can include:

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

Symptoms of pulmonary embolism (PE) can include:

- sudden onset of unexplained shortness of breath or rapid breathing
- sudden coughing which may be associated with haemoptysis
- sharp chest pain 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 nonspecific 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 CHCs with an increased risk for arterial thromboembolism (e.g. myocardial infarction, angina pectoris, stroke or TIA). Arterial thromboembolic events may be fatal.

The risk of arterial thromboembolic complications in CHC users increases in women with risk factors. LENEST 20 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 CHC should not be prescribed.

Risk Factors for ATE

- 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 CHC. 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 CHC use.

An increase in frequency or severity of migraine during CHC 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 CHC.

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 myocardial infarction (MI) can include:

- Pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone
- Discomfort radiating to the back, jaw, throat, arm, stomach
- Feeling of being full, having indigestion or choking
- Sweating, nausea, vomiting or dizziness
- Extreme weakness, anxiety, or shortness of breath
- Rapid or irregular heartbeats

Tumours

The most important risk factor for cervical cancer is persistent human papillomavirus (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 combined oral contraceptives. The excess risk gradually disappears during the course of the 10 years after cessation of combined oral contraceptive use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent combined oral contraceptive 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 combined oral contraceptive users, the biological effects of combined oral contraceptives 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 function may necessitate the discontinuation of COC 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 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 taking low dose COCs (containing < 50 µg ethinylestradiol). However, diabetic women 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 pink active tablet contains 74.83 mg of lactose monohydrate; each green placebo tablet contains 74.30 mg of lactose monohydrate. 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.

Check the Following Before Use

Medical Examination/Consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of COC use (guided by section 4.3 Contraindications and section 4.4 Special Warnings and Precautions for Use), and should be repeated periodically during the use of COCs. In general, an annual examination is recommended. 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 COC. The frequency and nature of these assessments should be based on established practice guidelines and be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests.

Sexually Transmitted Infections (STIs) including Human Immunodeficiency Virus (HIV) Infections and AIDS

LENEST 20 ED is intended to prevent pregnancy. It does not protect against STIs, including HIV infections (AIDS). The woman should be advised that additional barrier contraceptive measures are needed to prevent transmission of STIs.

Reduced Efficacy

The efficacy of COCs may be reduced in the event of missed pink active tablets, vomiting or diarrhoea during active tablet taking (see section 4.2 Dose and Method of Administration) or concomitant medication (see section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

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 interval. If the COC has been taken according to the directions described in section 4.2 Dose 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.

Alanine transaminase (ALT) elevations

In patients treated with hepatitis C antiviral medications including glecaprevir, pibrentasvir, ombitasvir, paritaprevir or dasabuvir, ALT elevations may occur in women using ethinylestradiol-containing medications such as CHCs. Prescribers should consult the relevant antiviral medicine product safety information. Patients taking a CHC should therefore be switched to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy.

Use in Hepatic Impairment

LENEST 20 ED is contraindicated in women with severe hepatic disease as long as liver function values have not returned to normal (see section 4.3 Contraindications).

Use in Renal Impairment

Levonorgestrel and ethinylestradiol tablets have not been specifically studied in renally impaired patients.

Use in the Elderly

LENEST 20 ED is not indicated after menopause.

Paediatric Use

LENEST 20 ED is only indicated after menarche.

Effects on 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

Effects of Other Medicines on Levonorgestrel and Ethinylestradiol Tablets

Interactions can occur with medicines that induce microsomal enzymes (e.g. cytochrome P450 enzymes, CYP34A) which can result in increased clearance of sex hormones and 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 prescribed 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 their discontinuation. If the period during which the barrier method is used runs beyond the end of the pink active tablets in the COC pack, the green placebo tablets should be omitted and the next COC pack be started.

Women taking interacting medications on a chronic basis should consider another method of contraception.

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 herbal medicines containing St John’s Wort (*Hypericum perforatum*).

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 concentration 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 Levonorgestrel and Eethinylestradiol Tablets on Other Medicines

Oral contraceptives may affect the metabolism of certain other medicines. Accordingly, plasma and tissue concentrations may either increase (e.g. ciclosporin) 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 ethinylestradiol-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 Contraindications and Section 4.4 Special Warnings and Precautions for Use). ALT elevations have also been observed with HCV anti-viral medicinal products including glecaprevir/pibrentasvir. Patients taking a CHC should therefore be switched to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy

Pregnancy category: B3

LENEST 20 ED is contraindicated during pregnancy. If pregnancy occurs during treatment with LENEST 20 ED, further intake must be stopped immediately.

Epidemiological studies have found no significant effects on fetal development 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

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Various adverse reactions have been associated with oral contraceptive use. The most commonly reported adverse reactions with levonorgestrel and ethinylestradiol tablets 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.

The most serious reactions associated with the use of oral contraceptives are discussed under section 4.4 Special Warnings and Precautions for Use.

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 on whether COC use should be discontinued.

Clinical Trial Data

Table 1 below displays the adverse events reported amongst patients in a clinical trial of levonorgestrel and ethinylestradiol tablets, for contraception (n = 805). It includes all adverse events reported with an incidence of 1% or greater. A total of 8.4% of women discontinued levonorgestrel and ethinylestradiol tablets therapy due to the adverse events. Intermenstrual bleeding and metrorrhagia (4%) were the study events most frequently reported as the reason for discontinuing levonorgestrel and ethinylestradiol tablets therapy. All other events that resulted in discontinuation were reported by less than 1% of the women.

Table 1

Adverse Event	Number of Women Affected	Percent of Women Affected
Gastrointestinal		
Nausea	63	7.8
Abdominal pain	31	3.8
Vomiting	14	1.7
Body as a Whole		
Flu Syndrome	9	1.1
Neurological		
Headache	142	17.6
Decreased libido	58	7.2
Migraine	47	5.8
Dizziness	40	5.0
Increased libido	29	3.6
Depression	22	2.7
Nervousness	17	2.1
Reproductive		
Breast pain	90	11.2
Intermenstrual bleeding/metrorrhagia	35	4.3
Breast tension	11	1.4

Skin		
Acne	62	7.7

A bioavailability study (n = 22) reported the following adverse events with a frequency of > 1%: intermenstrual bleeding 45%, headache/migraine 27%, dysmenorrhoea 23%, flu syndrome 18%, nausea 14%. A pharmacokinetic study (n = 18) reported the following adverse events with a frequency of > 1%: headache 78%, dysmenorrhoea 61%, flu syndrome 33%, common cold 28%, breast pain 17%.

Post-marketing Data

The following adverse events have been reported in users of low dose oral contraceptives and have been observed at the frequencies listed below but an association has neither been confirmed nor totally refuted:

- Very common ≥ 1 in 10 (≥10%)
- Common ≥ 1 in 100 and < 1 in 10 (between 1% and 10%)
- Uncommon ≥ 1 in 1000 and < 1 in 100 (between 0.1% and 1%)
- Rare ≥ 1 in 10000 and < 1 in 1000 (between 0.01% and 0.1%)
- Very rare < 1 in 10000 (<0.01%)

Table 2

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare
Infections and infestations		Vaginitis (candidiasis)			
Vascular				Venous and arterial thromboembolic events****	Aggravation of varicose veins
Gastrointestinal		Nausea Vomiting Abdominal pain	Abdominal cramps Bloating Diarrhoea		Pancreatitis Hepatic adenomas Hepatocellular carcinomas
Hepatobiliary				Cholestatic jaundice	Gallbladder disease (including gallstones*)
Metabolism/ Nutrition			Changes in appetite (increase or decrease)	Glucose intolerance	Exacerbation of porphyria
Psychiatric		Mood changes including depression, changes in libido			

Nervous	Headache including migraines	Nervousness Dizziness			Exacerbation of chorea
Skin and Subcutaneous Tissue		Acne	Rash Urticaria Cholasma (melasma) which may persist Hirsutism Alopecia	Erythema nodosum Erythema multiforme	
Eye				Intolerance to contact lenses	Optic neuritis[***] Retinal vascular thrombosis
Reproductive System and Breast	Metorrhagia (breakthrough bleeding and spotting)	Breast pain Tenderness Enlargement Secretion Dysmenorrhea Change in menstrual flow Change in cervical ectropion and secretion Vaginitis Amenorrhoea			
Renal and Urinary					Haemolytic uraemic syndrome
Immune				Anaphylactoid reactions including very rare cases of urticaria, angioedema and severe reactions with respiratory and circulatory systems	Exacerbation of systemic lupus erythematosus
General and Administration Site Reactions		Fluid retention/oedema			
Investigations		Changes in weight	Increase in blood pressure	Decrease in serum folate levels[**]	

		(increase or decrease)	Changes in serum lipid levels including hypertriglyceridaemia		

[*] Oral contraceptives may worsen existing gall bladder disease and may accelerate the development of this disease in previously asymptomatic women

[**] Serum folate levels may be depressed by oral contraceptive therapy

[***] Optic neuritis may lead to partial or complete loss of vision

[****] Estimated frequency, from epidemiological studies encompassing a group of combined oral contraceptives

'Venous and arterial thromboembolic events' summarises 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.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There have been no reports of serious deleterious effects from overdose. Symptoms that may occur in this case are: nausea, vomiting and withdrawal bleeding. The last may even occur in girls before their menarche, if they have accidentally taken the medicinal product. There are no antidotes and further treatment should be symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

The hormonal components of the tablets inhibit ovulation by suppressing gonadotrophin release. Secondary mechanisms which may contribute to the effectiveness of LENEST 20 ED as a contraceptive include changes in the cervical mucus (which increase the difficulty of sperm penetration) and changes in the endometrium (which reduce the likelihood of implantation).

Clinical Trials

An open-label, non-comparative multi-centre phase III clinical study was conducted in 820 women receiving levonorgestrel and ethinylestradiol tablets for a planned individual maximum of 6 cycles. Six cycles were completed by 680 women. 4,400 cycles in which no alternative methods of contraception were used were available for the efficacy analysis. One pregnancy was reported. This represents an overall user-efficacy (typical user-efficacy) pregnancy rate of 0.32 per 100 women years (over 99% effective at preventing pregnancy). This rate includes patients who missed up to 3 tablets per cycle. The overall compliance (no

missed tablets) was between 94.6% and 98.4% over the course of the study. Published data from a larger study with a similar preparation containing the same dosage of active ingredients in 1447 women, with 7720 cycles of exposure, reports 5 pregnancies and an overall user-efficacy pregnancy rate of 0.84 per 100 women years, in women who missed up to 3 tablets consecutively per cycle or 5 non-consecutive tablets per cycle.

The overall user-efficacy pregnancy rates for levonorgestrel and ethinylestradiol tablets and other forms of contraception from a number of non-comparative trials based on historical data are given in table 3 below:

Table 3

Oral Contraceptive	Overall User Efficacy (Pearl Index)	Effectiveness* at Preventing Pregnancy
100 µg levonorgestrel 20 µg ethinylestradiol	0.32	99.68%
100 µg levonorgestrel 20 µg ethinylestradiol	0.84	99.16%
150 µg levonorgestrel 30 µg ethinylestradiol	0.30 – 0.35	99.65 – 99.7%
30 µg ethinylestradiol	0.30 – 3.0	97.00 – 99.7%

*100%-(Pearl Index) = User effectiveness per 100 women years. (e.g if 100 women took oral contraceptive tablets for 1 year the chance of an accidental pregnancy would be less than 1%).

Whilst the contraceptive efficacy of levonorgestrel and ethinylestradiol tablets was 99.68% in a single study, the contraceptive efficacy of the levonorgestrel 100 µg/ethinylestradiol 20 µg formulations ranges from 99.16 - 99.68%, compared historically with the contraceptive efficacy of 99.7% for 150 µg levonorgestrel/30 µg ethinylestradiol tablets, this represents a similar up to 2-fold increase in the risk of pregnancy.

Cycle control was also evaluated by analysing cycle characteristics such as duration and intensity of withdrawal bleeding and the incidence of breakthrough bleeding and amenorrhoea. A total of 4400 cycles were valid for cycle control analysis; the overall incidence of inter-menstrual bleeding was low. Although there was no comparative study of the cycle control of levonorgestrel and ethinylestradiol tablets, compared with higher dosage oral contraceptives, cycle control data from historical studies with oral contraceptives containing higher doses of ethinylestradiol and levonorgestrel are given in table 4 below:

Table 4

Dose*/ Study	Number of Women	Number of Cycles	Breakthrough Bleeding (% cycles)	Spotting (% cycles)	Amenorrhoea (% cycles)	Cycle Length (days)	Mean Length of Menstruation (days)
100/20 levonorgestrel/ ethinylestradiol (6 cycles)	820	4400	4.5	12.4	4.5	26 – 30	4.7
150/30	1130	11064	6.0	7.7	1.8	26 – 30 (mean 28.5)	4.3
150/30	325	3445	0.7	2.7	0.6	27 – 29	-

* Dose of levonorgestrel (µg)/ethinylestradiol (µg). Note that the definitions of bleeding in these studies are not necessarily the same.

The length of withdrawal bleeding was 3 to 5 days for most patients (70%) (mean 4.7 days) and the intensity was scanty or normal for most subjects. Cycle length was between 26 and 30 days for most patients (up to 80%) with a tendency to be slightly shorter during the early cycles.

5.2 PHARMACOKINETIC PROPERTIES

A bioavailability study comparing levonorgestrel and ethinylestradiol tablets to a microcrystalline solution was conducted. However, as this study employed doses equivalent to three tablets instead of single tablet dosing for technical reasons, the pharmacokinetic information provided is derived from a single tablet pharmacokinetic study conducted in 20 women.

Levonorgestrel

Absorption

Levonorgestrel is absorbed quickly and completely. Maximum active substance levels of approx. 2.4 ng/mL were reached in serum approximately 1.0 to 1.3 hours after ingestion of levonorgestrel and ethinylestradiol tablets. The absolute bioavailability of levonorgestrel amounts to almost 100%.

Distribution

Levonorgestrel is bound to serum albumin and sex hormone binding globulin (SHBG). Only around 1.1% of the respective total concentration is present in unbound form, while approximately 65% is bound to SHBG. The relative proportions (free, albumin-bound, SHBG-bound) depend on the concentration of SHBG. After induction of the binding protein, the portion bound to SHBG increases to 75%, while the free portion and that bound to albumin decrease to around 0.8 and 25%, respectively.

Metabolism

Extensive reduction of the α, β-unsaturated ketone in ring A occurs, in addition to hydroxylation at carbons 2 and 16 to form dihydro and tetrahydro reduced products. Metabolites may circulate as sulfates or glucuronides, however most of the metabolites that circulate in the blood are sulfates of 3α, 5β-tetrahydro-levonorgestrel. There are also large amounts of unconjugated levonorgestrel in the circulation with small amounts of unconjugated and/or conjugated forms of 3α, 5β-tetrahydrolevonorgestrel and 16β-hydroxylevonorgestrel. Excretion occurs predominantly in the form of glucuronides.

The metabolic clearance rate, including the bound component, from plasma is approximately 1.0 mL/min/kg.

Elimination

The serum concentrations subsequently fall in at least 2 disposition phases with a terminal half-life of around 24 hours.

Levonorgestrel is eliminated not in unchanged form, but in the form of metabolites with a half-life of approximately 28 ± 7 hours and in almost equal proportions via the kidney and bile.

Steady-State Conditions

After daily repeated ingestion, levonorgestrel accumulates by about the factor of 3. A steady state is reached after approximately 11 days. The pharmacokinetics of levonorgestrel are nonlinear due to an increase in binding of levonorgestrel to SHBG which is attributed to increased SHBG levels that are induced by the daily administration of ethinylestradiol. The levonorgestrel serum levels do not change any further after 1 to 3 cycles of use because SHBG induction is concluded.

Ethinylestradiol

Absorption

Orally administered ethinylestradiol is absorbed quickly and almost completely from the gastrointestinal tract but due to first-pass metabolism in gut mucosa and liver, the absolute bioavailability of ethinylestradiol is subject to considerable interindividual variations. After oral ingestion, it amounts to around 40 to 60% of the dose.

Ingestion of levonorgestrel and ethinylestradiol tablets leads to maximum plasma levels of approx. 50 pg/mL after 1 to 2 hours. The substance concentration then falls in at least 2 disposition phases with a terminal half-life of around 24 hours. For technical reasons, these data can only be calculated at higher dosages.

Distribution

Ethinylestradiol is bound non-specifically to serum albumin to about 98%. Ethinylestradiol does not bind to SHBG but induces SHBG synthesis.

Metabolism

Cytochrome P450 enzymes (CYP3A4) in the liver are responsible for the 2-hydroxylation that is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and faecal excretion. Levels of CYP3A4 vary widely amongst individuals and may explain the variations in rates of ethinylestradiol 2-hydroxylation. Ethinylestradiol is excreted in the urine and faeces as glucuronide and sulfate conjugates and undergoes enterohepatic circulation.

Elimination

Ethinylestradiol is eliminated not in unchanged form, but in the form of metabolites with a half-life of around 18 ± 4.7 hours at steady state. The excretion ratio is 40 (urine): 60 (bile).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

There is limited evidence available in the literature suggesting that estrogens may be weakly genotoxic at high doses. Ethinylestradiol was negative in studies for DNA-adduct formation in cultured human liver slices and in assays for gene mutations (bacterial or mammalian cells *in vitro*) and gave equivocal results in assays for chromosomal damage (clastogenic effects were not consistently seen and occurred at high doses).

The genotoxic potential of levonorgestrel has not been fully investigated, although limited data available to date suggest that it did not appear to be genotoxic.

Carcinogenicity

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis and liver. A long-term study with levonorgestrel in dogs showed an increased incidence of mammary tumours, although a similar effect was not apparent in studies in mice, rats or monkeys. The occurrence of these mammary tumours in dogs may be due in part to a hormonal feedback mechanism. The clinical relevance of these findings is uncertain.

Numerous epidemiological studies have been conducted to determine the incidence of breast, endometrial, ovarian and cervical cancer in women taking combination oral contraceptives. Some of these studies have shown an increased relative risk of breast cancer in certain subgroups of combination oral contraceptive users. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms should be monitored with particular care. Benign hepatic adenomas have been found to be associated with the use of oral contraceptives. Although benign, hepatic adenomas may rupture and cause death through intra-abdominal haemorrhage. Some epidemiological studies also suggest that combination oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women, although 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 HPV. It must also be borne in mind that sexual steroids can promote the growth of certain hormone-dependent tissues and tumours (see section 4.4 Special Warnings and Precautions for Use).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The pink active tablets contain the following excipients: lactose monohydrate, magnesium stearate, povidone, iron oxide red, microcrystalline cellulose, croscarmellose sodium and sodium lauryl sulfate.

The green placebo tablets contain the following excipients: lactose monohydrate, magnesium stearate, povidone, microcrystalline cellulose, croscarmellose sodium, iron oxide yellow and brilliant blue FCF aluminium lake.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Store in the original container.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: blister pack (PVC/PVDC/Al)

Pack sizes: 1 x 28 tablets, 2 x 28 tablets, 3 x 28 tablets or 4 x 28 tablets. The 28-tablet blister sheet contains 21 round pink active tablets and 7 round green placebo tablets.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 219146 – LENEST 20 ED levonorgestrel/ethinylestradiol 100 microgram/20 microgram tablet blister composite pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

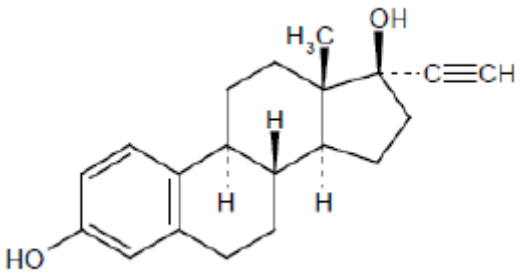
Ethinylestradiol

Ethinylestradiol is a white to creamy white, odourless, crystalline powder.

Ethinylestradiol is insoluble in water and soluble in alcohol, chloroform, ether, vegetable oils and aqueous solutions of alkali hydroxides.

Chemical name: 19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3, 17β-diol

Structural formula:



Molecular Formula: $C_{20}H_{24}O_2$

Molecular Weight: 296.41

Melting Point: 181-185°C

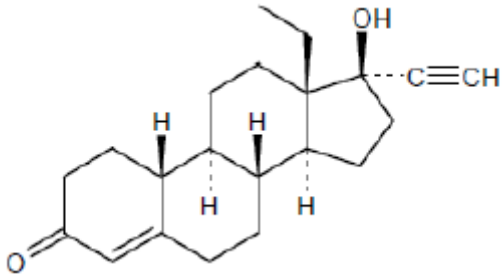
Levonorgestrel

Levonorgestrel is practically insoluble in water; slightly soluble in alcohol, acetone and ether; soluble in chloroform; sparingly soluble in methylene chloride.

Levonorgestrel is a white or almost white, odourless or almost odourless, crystalline powder.

Chemical name: 13β-ethyl-17β-hydroxy-18, 19-dinor-17α-pregn-4-en-20-yn-3-one

Structural formula:



Chemical Formula: $C_{21}H_{28}O_2$

Molecular Weight: 312.45

Melting Point: 232-239°C

CAS Number

Ethinylestradiol: 57-63-6

Levonorgestrel: 797-63-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

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Millers Point NSW 2000

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Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

21/11/2014

10 DATE OF REVISION

29/06/2023

References

1. Dinger JC, Heinemann LA, Kuhl-Habich D. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance study on Oral Contraceptives based on 142,475 women-years of observation. Contracept 2007; 75:344-54.

2. Long-term Active Surveillance Study for Oral contraceptives (LASS), 2nd update report based on study status. May 2009.

Summary Table of Changes

Section Changed	Summary of New Information
4.3, 4.4, 4.5	Update to anti-viral contraindications
2, 3, 6.1, 6.4, 6.5	Editorial Changes
8	Update to sponsor details

Lenest 20 ED_pi\Jun23/01