AUSTRALIAN PRODUCT INFORMATION - LOETTE® (LEVONORGESTREL AND ETHINYLESTRADIOL) TABLETS

1. NAME OF THE MEDICINE

Levonorgestrel and Ethinylestradiol

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pink tablet contains levonorgestrel 100 μg and ethinylestradiol 20 μg.

Each white tablet contains no active ingredients.

Excipients with known effect

- Lactose monohydrate

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

3. PHARMACEUTICAL FORM

Tablet, film coated.

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Pink tablet: Round, pink, biconvex, film coated tablets with "W" debossed on one side and "912" debossed on the other side.

White tablet: White film-coated round tablet with convex faces.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LOETTE is indicated for:

The prevention of pregnancy.

The treatment of moderate acne vulgaris not controlled with topical preparations in post-menarchal, pre-menopausal women who accept contraception.

4.2 Dose and method of administration

How to Take LOETTE

Each package of LOETTE contains 21 active pink tablets and 7 white inactive tablets.

To achieve maximum contraceptive effectiveness, LOETTE must be administered as directed and at the same time every day, at intervals not exceeding 24 hours. The recommended dose for the prevention of pregnancy and the treatment of acne is the same.

Where poor compliance is a concern, an oral contraceptive with higher levels of estrogens and progestogens should be considered (see section 5.1, Pharmacodynamic Properties, Clinical Trials).

How to Start LOETTE

No Preceding Hormonal contraceptive Use (in the Past Month)

On the first day of the menstrual cycle, i.e. the first day of bleeding, the woman is instructed to take a pink active tablet corresponding to that day of the week from the pink shaded section of the LOETTE pack. Thereafter, one pink active tablet is taken daily, following the arrows marked on the package, until all 21 pink active tablets have been taken. The woman is then instructed to take one white inactive tablet daily for the next seven days following the arrows marked on the LOETTE pack. Withdrawal bleeding should usually occur within 2 to 4 days after the last pink active tablet is taken.

LOETTE is effective for contraception from the first day of therapy if the tablets are begun on Day 1 as described. If starting on days 2-7 of menstrual bleeding, a back-up method of contraception is recommended for the first 7 days of tablet taking.

The back-up method of contraception must be an additional non-hormonal barrier method such as condoms or a diaphragm with a spermicide. Back-up contraception does not include the rhythm or temperature methods.

The next and all subsequent courses of LOETTE will begin on the day after the last package was completed, even if withdrawal bleeding is still in progress. Each course of LOETTE is thus begun on the same day of the week as the first course.

Any time a new cycle of LOETTE is started later than the eighth day after discontinuation of the pink active tablet, the woman should use a back-up method of contraception (other than the rhythm or temperature methods), until an active pink tablet has been taken for 7 consecutive days.

Missed Withdrawal Bleed

If withdrawal bleeding does not occur and LOETTE has been taken according to directions, and conditions possibly impairing contraceptive effectiveness (refer to section 4.4, Special Warnings and Precautions for Use - Vomiting and/or Diarrhoea and section 4.5, Interaction With Other Medicines and Other Forms of Interactions) can be ruled out, it is unlikely that the woman has conceived. She should be instructed to begin a second course of LOETTE on the usual day. If bleeding does not occur at the end of this second cycle, LOETTE should not be taken until diagnostic procedures to exclude the possibility of pregnancy have been performed.

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

Changing from another Combined Oral Contraceptive

The woman is advised to take the first pink LOETTE tablet from the pink shaded section, which corresponds to the day of the week on the day after the last active tablet from her previous oral contraceptive. However, the woman can also begin LOETTE on any day during the tablet free or inactive tablet interval of her previous combined oral contraceptive.

During the first LOETTE cycle, a non-hormonal back-up method of contraception (other than the rhythm or temperature methods) should be used until one active tablet has been taken daily for 7 consecutive days. When changing to LOETTE a woman should be reminded about the importance of compliance in order to maximise contraceptive efficacy (see section 5.1, Pharmacodynamic Properties, Clinical Trials).

If transient spotting or breakthrough bleeding occurs, the woman is instructed to continue the regimen since such bleeding is usually without significance. If the bleeding is persistent or prolonged, the woman is advised to consult her physician.

Changing from a Progestogen Only Method (Progestogen Only Tablets, Injection, Implant)

The woman may switch any day from progestogen-only tablets and should begin LOETTE the next day. She should start LOETTE on the day of an implant removal or, if using an injection, on the day the next injection would be due. In all of these situations, the woman should be advised to use a non-hormonal back-up method of contraception (other than the rhythm or temperature methods) until one active tablet has been taken daily for 7 consecutive days.

How to Delay a Withdrawal Bleed

To delay a withdrawal bleed the woman should discard the inactive white tablets from the current pack and start the next pack on the day following the intake of the last pink tablet from the current pack. The extension can be carried on for as long as wished until the end of the second pack, when the white tablets are taken. During the extension the woman may experience breakthrough bleeding or spotting. Regular intake of LOETTE is then resumed with the next pack.

Following First Trimester Abortion

The woman may start LOETTE immediately. Additional contraceptive measures are not needed.

Following Delivery or Second-Trimester Abortion

Since the immediate post-partum period is associated with an increased risk of thromboembolism, LOETTE should be started no earlier than day 28 after delivery in the non-lactating mother or after second-trimester abortion. The woman should be advised to additionally use a back-up method of contraception (other than the rhythm or temperature methods) until one active tablet has been taken daily 7 consecutive days. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of LOETTE use or the woman has to wait for her first menstrual withdrawal bleed (see section 4.4, Special Warnings and Precautions for Use, Venous Thrombosis

and Thromboembolism, and section 4.6, Fertility, Pregnancy and Lactation, Use in Pregnancy and Use in Lactation).

Management of Missed Tablets

Contraceptive efficacy may be reduced if tablets are missed and particularly if the missed tablets extend the inactive tablet interval. If tablets were missed in the first week of the cycle and intercourse took place in the week before the tablets were missed, the possibility of a pregnancy should be considered.

If one active pink is missed, but is less than 12 hours late**,** it should be taken as soon as it is remembered. Subsequent tablets should be taken at the usual time.

If one active pink tablet is missed and is more than 12 hours late or if more than one active tablet is missed contraceptive protection may be reduced. The last missed pink tablet should be taken as soon as it is remembered, even if this means taking two active pink tablets in one day. Any earlier missed tablets should be discarded. The woman should then continue to take tablets at her usual time. In addition, a non-hormonal back-up method of contraception (other than the rhythm or temperature methods) should be used until one active tablet has been taken daily for 7 consecutive days.

If the 7 days where back-up is required run beyond the last active pink tablet in the current pack, the next pack must be started on the day following the intake of the last pink tablet in the current pack. All inactive (white) tablets should be discarded. This prevents an extended break in the active tablet taking that may increase the risk of escape ovulation. The woman is unlikely to have a withdrawal bleed until the inactive-tablet interval of the second pack, but she may experience spotting or breakthrough bleeding on days when active tablets are taken. If the woman does not have a withdrawal bleed at the end of the second pack, the possibility of pregnancy must be ruled out before resuming tablet taking.

If the woman misses one or more white inactive tablets, she will still be protected against pregnancy provided she begins the pink active tablets on the appropriate day.

Vomiting or Diarrhoea

If vomiting or diarrhoea occurs during or shortly after the intake of LOETTE, contraceptive reliability may be jeopardised. If vomiting or diarrhoea occurs within 3 to 4 hours after tablet taking, absorption may not be complete. In such an event, the advice concerning ***Management of Missed Tablets*** is applicable. The woman must take the extra active tablet(s) needed from a back-up pack.

4.3 Contraindications

LOETTE 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 LOETTE use, the product should be stopped immediately.

- Presence or risk of venous thromboembolism (VTE) (see section 4.4, Special Warnings and Precautions for Use).
  - A history of or current deep-vein thrombosis or thromboembolic disorders.

- 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]) or thrombogenic valvulopathies or thrombogenic rhythm disorders.
  - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (e.g. anticardiolipin-antibodies and lupus anticoagulant).
  - Headaches with focal neurological symptoms (such as aura) including hemiplegic migraine.
  - 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.
    - Uncontrolled hypertension.
    - Disorders of lipid metabolism.
    - Sickle cell anaemia.
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia.
- Presence or history of active hepatic disease as long as liver function values have not returned to normal.
- Presence or history of liver tumours (benign or malignant).
- Idiopathic cholestatic jaundice of pregnancy or jaundice with prior combined oral contraceptive use.
- Known or suspected sex steroid-influenced malignancies (e.g. of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Combined oral contraceptives are contraindicated for concomitant use with certain anti-viral hepatitis C virus (HCV) medicinal products such as ombitasvir, paritaprevir, ritonavir and dasabuvir (see section 4.4, Special Warnings and Precautions for Use, Hepatic neoplasia/Liver Disease/Hepatitis C and section 4.5, Interactions With Other Medicines and Other Forms of Interactions).
- Hypersensitivity to any of the ingredients contained in LOETTE.

4.4 Special warnings and precautions for use

The information contained in this document is principally based on studies carried out in women who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower doses of both estrogens and progestogens remains to be determined.

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

Circulatory Disorders

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

For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient.

Venous Thrombosis and Thromboembolism

Risk of venous thromboembolism (VTE)

The use of any COC increases the risk of VTE compared with no use. The women considering using LOETTE 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.

The risk of VTE with the COC is greatest for products containing over 50 µg of ethinylestradiol. There is less risk for products such as LOETTE containing less than 35 µg ethinylestradiol.

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.

Risk1 of developing a blood clot (VTE) in a year

Women not using a combined hormonal contraceptive and not pregnant	About 2 out of 10,000 women[1]
Women using a COC containing levonorgestrel, norethisterone or norgestimate	About 5-7 out of 10,000 women
Women using a COC containing etonogestrel or norelgestromin	About 6-12 out of 10,000 women

Women using a COC containing drospirenone, gestodene, desogestrel or cyproterone[2]	About 9-12 out of 10,000 women
Women using a COC containing chlormadinone, dienogest or nomegestrol	Not yet known[3]

[1] In any individual woman the risk may be far higher, depending on her underlying risk factors (see below).[2] While cyproterone is indicated for the treatment of moderate to severe acne related to androgen sensitivity and/or hirsutism, it is known to have efficacy as a contraceptive. The risk of VTE associated with cyproterone use is considered to be 1.5 to 2 times higher than for COCs containing levonorgestrel and may be similar to the risk with contraceptives containing gestodene, desogestrel or drospirenone.

[3] Further studies are ongoing or planned to collect sufficient data to estimate the risk for these products. Where the risk for a particular progestogen is uncertain, the risk of the class should be used in determining the risk for the individual patient.

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.

However VTE is a serious condition and may be fatal 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).

LOETTE 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.

Risk factors for VTE

The risk of venous thrombotic and thromboembolic events is further increased in women with conditions predisposing for venous thrombosis and thromboembolism. Examples of predisposing conditions for venous thrombosis and thromboembolism are:

- 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 Activated Protein C (APC) resistance (including Factor V Leiden), antithrombin-III deficiency, protein C deficiency, protein S deficiency.
- Other medical conditions associated with VTE:
  - 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.
- Recent delivery or second trimester abortion.
- 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 LOETTE (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 LOETTE 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.

The increased risk of VTE during the postpartum period should be considered if re-starting LOETTE.

Since the immediate post-partum period is associated with an increased risk of thromboembolism, combined oral contraceptives should be started no earlier than day 28 after delivery in a non-lactating woman, or second-trimester abortion.

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

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 COC.

Symptoms of deep vein thrombosis (DVT) can include:

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

Symptoms of pulmonary embolism (PE) can include:

- Sudden onset of unexplained shortness of breath or rapid breathing.
- Sudden coughing which may be associated with haemoptysis.
- Sharp chest pain.
- Severe light headedness or dizziness.

- Rapid or irregular heartbeat.

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

Other signs of vascular occlusion can include: sudden pain, swelling and slight blue 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.

Arterial Thrombosis and Thromboembolism

Risk of arterial thromboembolism (ATE)

Epidemiological studies have associated the use of COCs with an increased risk for arterial thrombotic and thromboembolic events (e.g. myocardial infarction, angina pectoris, and cerebrovascular events, such as ischaemic and haemorrhagic ischemic and haemorrhagic stroke or TIA). Arterial thromboembolic events may be fatal.

The risk of arterial thrombotic and thromboembolic complications in COC users further increases in women with risk factors. LOETTE 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.

Risk factors for ATE

Caution must be exercised when prescribing COCs for women with risk factors for arterial thrombotic and thromboembolic events, such as:

- Increasing age, particularly above 35 years.
- Smoking.
- Hypertension.
- Hyperlipidaemias.
- Obesity.
- Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g. below 50).
- Biochemical factors: 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.
- History of pre-eclamptic toxaemia.

Cigarette smoking increases the risk of serious cardiovascular adverse reactions from COC use. This risk increases with age and with the extent of smoking (in epidemiology studies, smoking 15 or more cigarettes per day was associated with a significantly increased risk), and is quite marked in women over 35 years of age. Women should be advised not to smoke if they wish to use a COC. Women over 35 years of age 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.

The onset or exacerbation of migraine or development of headache of a new pattern that is recurrent, persistent, or severe, requires discontinuation of the medicine and evaluation of the cause.Women with migraine (particularly migraine with aura) who take combined oral contraceptives may be at increased risk of stroke.

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, trouble speaking or understanding.
- Sudden trouble seeing in one or both eyes.
- Sudden, severe or prolonged headache with no known cause.
- Loss of consciousness or fainting with or without seizure.

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

Symptoms of myocardial infarction (MI) can include:

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

Medical Examination/Consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of COC use, guided by the contraindications and precautions, and should be repeated at least annually during the use of COCs. Pregnancy should be ruled out before the start of therapy. A Papanicolaou (Pap) smear should be performed if the patient has been sexually active or if it is otherwise indicated. 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 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.

The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given.

Carcinoma of the Reproductive Organs

Cervical Cancer

The most important risk factor for cervical cancer is persistent human papillomavirus infection.

Several epidemiological studies suggest that oral contraceptive use may be associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer. The studies suggest that there is an "ever used" effect in addition to duration of use. These findings must be balanced against evidence of effects attributable to sexual behaviour, smoking and other factors. In cases of undiagnosed abnormal genital bleeding, adequate diagnostic measures are indicated.

Breast Cancer

A meta-analysis from 54 epidemiological studies showed that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using combined oral contraceptives compared to never-users. The increased risk gradually disappears during the course of the 10 years after cessation of combined oral contraceptive use. 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 (due to more regular clinical monitoring), the biological effects of combined oral contraceptives or a combination of both. 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 lifetime risk of breast cancer. Breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

Established risk factors for the development of breast cancer include increasing age, family history, obesity, nulliparity, and late age for first full-term pregnancy.

Women with a strong family history of breast cancer or who have breast nodules, fibrocystic breast disease or abnormal mammograms should be monitored with particular care.

Hepatic Neoplasia/Liver Disease/Hepatitis C

In very rare cases hepatic adenomas, and in extremely rare cases, hepatocellular carcinoma may be associated with combined oral contraceptives use. The risk appears to increase with duration of combined oral contraceptive use. Hepatic adenomas may rupture and cause death through intra-abdominal haemorrhage. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen and should be considered if the patient has abdominal pain and tenderness or evidence of intra-abdominal bleeding.

Women with a history of COC-related cholestasis and women who develop cholestasis during pregnancy are more likely to develop cholestasis with COC use. Such patients who use COCs should be carefully monitored, and COC use should be discontinued if cholestasis recurs.

Hepatocellular injury has been reported with combined oral contraceptive use. Early identification of drug-related hepatocellular injury can decrease the severity of hepatotoxicity when the drug is discontinued. If hepatocellular injury is diagnosed, patients should stop their combined oral contraceptive use, use a non-hormonal form of contraception and consult their doctor.

Acute or chronic disturbances of liver function require the discontinuation of combined oral contraceptive use until liver function has returned to normal (see section 4.3, Contraindications).

Steroid hormones may be poorly metabolised in patients with impaired liver function.

Hepatitis C

During clinical trials with patients treated for HCV infections with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequently in women using ethinylestradiol-containing medications such as COCs (see sections 4.3, Contraindications and 4.5, Interactions With Other Medicines and Other Forms of Interactions**)**.

Ocular Lesions

With the use of combined oral contraceptives, there have been case reports of retinal thrombosis, which may lead to partial or complete loss of vision. Oral contraceptives should be discontinued and the cause immediately evaluated if there are signs or symptoms such as visual changes; onset of proptosis or diplopia; papilloedema, or retinal vascular lesions.

Gallbladder Disease

Combined oral contraceptives may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.

Carbohydrate and Lipid Metabolic Effects

Evidence from clinical trials with LOETTE indicates that there are no clinically significant changes in carbohydrate metabolism parameters.

Glucose intolerance has been reported in oral contraceptives users. In particular, some progestogens are known to increase insulin secretion and create insulin resistance, while estrogens (>75 micrograms) may create a state of hyperinsulinism. However, in the non-diabetic woman, low dose oral contraceptives appear to have no effect on fasting blood glucose. Women with

impaired glucose tolerance or diabetes mellitus should be carefully monitored while taking oral contraceptives.

A small proportion of women will have adverse lipid changes while taking OCs. Non-hormonal contraception should be considered in women with uncontrolled dyslipidaemias.

A small proportion of women may have persistent hypertriglyceridaemia while taking oral contraceptive tablets. Elevations of plasma triglycerides in combined oral contraceptive users may lead to pancreatitis and other complications.

Estrogens increase serum high-density lipoproteins (HDL cholesterol), whereas a decline in serum HDL cholesterol has been reported with many progestational agents. Some progestogens may elevate low-density lipoprotein (LDL) levels and may render the control of hyperlipidaemias more difficult. The net effect of a combined oral contraceptive depends on the balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogen used in the contraceptive. The amount of both hormones should be considered in the choice of acombined oral contraceptive.

Women who are being treated for hyperlipidaemias should be followed closely if they elect to use combined oral contraceptives (see section 4.3, Contraindications).

Elevated Blood Pressure

An increase in blood pressure has been reported in women taking oral contraceptives and this increase is more likely in older oral contraceptive users and with continued use.

In women with hypertension, or a history of hypertension or hypertension-related diseases (including certain renal diseases), another method of contraception may be preferable. If combined oral contraceptives are used in such cases, close monitoring is recommended. If a significant elevation of blood pressure occurs, the drug should be discontinued.

For most women, elevated blood pressure will generally return to baseline after stopping combined oral contraceptives, and there appears to be no difference in the occurrence of hypertension among ever- and never- users.

Combined oral contraceptive use is contraindicated in women with uncontrolled hypertension.

Angioedema

Exogenous estrogens may induce or exacerbate symptoms of angioedema, particularly in women with hereditary angioedema.

Genital Bleeding

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. The type and dose of progestogen may be important. If this bleeding persists or recurs, non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy, infection, pregnancy or other conditions. If pathology has been excluded, continued use of LOETTE or a change to another formulation may solve the problem.

In some women, withdrawal bleeding may not occur during the usual inactive tablet interval. If LOETTE has been taken according to directions, it is unlikely that the woman is pregnant. However, if LOETTE has not been taken according to directions prior to the first missed withdrawal bleed or if two consecutive withdrawal bleeds are missed, tablet taking should be discontinued and a non-hormonal back-up method of contraception should be used until the possibility of pregnancy is excluded.

Some women may encounter post-tablet amenorrhoea (possibly with anovulation), or oligomenorrhoea, especially when such a condition was pre-existent.

Precautions for Patients with Other Existing Pathology

The following conditions have been reported to occur or deteriorate with combined oral contraceptive use: sickle cell anaemia, multiple sclerosis, epilepsy, otosclerosis, herpes gestationis, systemic lupus erythematosus and renal dysfunction, but evidence for an association of these conditions with combined oral contraceptive use is inconclusive. These conditions require careful monitoring during the use of combined oral contraceptives. Deterioration of these conditions may indicate that LOETTE be discontinued. When prescribing combined oral contraceptives for women with any of the above conditions, the risks and benefits of alternate contraceptive methods should be considered.

Vomiting and/or Diarrhoea

Diarrhoea and/or vomiting may reduce hormone absorption resulting in decreased serum concentrations (see section 4.2, Dose and Method of Administration).

Folate Levels

Serum folate levels may be depressed by oral contraceptive use. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

Depression

Patients becoming significantly depressed while taking LOETTE should stop the medication and use an alternative method of contraception in an attempt to determine whether the symptom is drug-related. Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

Chloasma

In predisposed women, use of an oral contraceptive may sometimes cause chloasma, which is aggravated by exposure to the sun. Women who have this tendency should therefore avoid prolonged exposure to the sun.

HIV Infection

Patients should be counselled that LOETTE does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Contraceptive Efficacy

LOETTE is a low dose oral contraceptive. To ensure optimal contraceptive efficacy, it is important that LOETTE is taken strictly as directed. A non-hormonal back-up method of contraception (other than the rhythm or temperature methods) should also be used in any instance where the tablets are not taken as directed (see section 4.2, Dose and Method of Administration).

Use in the Elderly

Combined oral contraceptives are not indicated for use in postmenopausal women.

Paediatric Use

Safety and efficacy of combined oral contraceptives have been established in women of reproductive age. Use of these products before menarche is not indicated.

Effects on Laboratory Tests

The use of oral contraceptives may influence the results of certain laboratory tests including:

- Biochemical parameters of liver function (including a decrease in bilirubin and alkaline phosphatase), thyroid function (increased total T3 and T4 due to increased TBG, decreased free T3 resin uptake), adrenal function (increased plasma cortisol, increased cortisol binding globulin,), decreased dehydroepiandrosterone sulfate (DHEAS), and renal function (increased plasma creatinine and creatinine clearance).
- Plasma levels of (carrier) proteins, such as corticosteroid-binding globulin and lipid/lipoprotein fractions.
- Parameters of carbohydrate metabolism.
- Parameters of coagulation and fibrinolysis.
- Decreased serum folate levels.

4.5 Interactions with other medicines and other forms of interactions

Interactions between ethinylestradiol and other substances may lead to decreased or increased ethinylestradiol concentrations, respectively.

Concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (see section 4.3, Contraindications and section 4.4, Special Warnings and Precautions for Use, Hepatic Neoplasia/Liver Disease/Hepatitis C).

Therefore, COC users must switch to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy with anti-viral HCV medicinal products such as ombitasvir, paritaprevir, ritonavir, dasabuvir. COCs can be restarted 2 weeks following completion of treatment with an anti-viral HCV medicinal product.

Decreased ethinylestradiol serum concentrations may cause an increased incidence of breakthrough bleeding and menstrual irregularities and may possibly reduce efficacy of the oral contraceptive.

Examples of substances that may decrease serum ethinylestradiol concentrations include:

- Any substance that reduces gastrointestinal transit time and, therefore, ethinylestradiol absorption.

- Substances that induce hepatic microsomal enzymes, such as rifampicin, phenytoin, carbamazepine, primidone, rifabutin, dexamethasone, griseofulvin, topiramate, some protease inhibitors, modafinil, ritonavir and barbiturates.

- St. John's Wort (*Hypericum perforatum*) may induce hepatic microsomal enzymes, which may result in reduced efficacy of oral contraceptives. This may also result in breakthrough bleeding.

- Certain antibiotics including ampicillin, other penicillins and tetracyclines may reduce the efficacy of oral contraceptives by decreasing enterohepatic circulation of estrogens.

During concomitant use of LOETTE and substances that may lead to decreased ethinylestradiol serum concentrations, it is recommended that a non-hormonal back-up method of contraception (other than the rhythm or temperature methods) be used in addition to the regular intake of LOETTE. In the case of prolonged use of such substances combined oral contraceptives should not be considered the primary contraceptive.

After discontinuation of substances that may lead to decreased ethinylestradiol serum concentrations, use of a non-hormonal back-up method of contraception is recommended for at least 7 days.

Longer use of a back-up method, a minimum of 4 weeks, is advisable after discontinuation of substances that have led to induction of hepatic microsomal enzymes, resulting in decreased ethinylestradiol serum concentrations, such as rifampicin. It may sometimes take several weeks until enzyme induction has completely subsided, depending on dosage, duration of use and rate of elimination of the inducing substance.

There have been reports of pregnancy when COCs were co-administered with certain antibiotics (e.g., ampicillin and other penicillins, tetracyclines).

Examples of substances that may increase serum ethinylestradiol concentrations include:

- Atorvastatin.

- Competitive inhibitors for sulfation in the gastrointestinal wall, such as ascorbic acid (vitamin C) and paracetamol.

- Substances that inhibit cytochrome P-450 3A4 isoenzymes (e.g. itraconazole, fluconazole, and indinavir).

Ethinylestradiol may inactivate certain CYP450 enzymes and may therefore reduce the metabolism of other drugs. It may also induce hepatic drug conjugation, particularly glucuronidation. Accordingly, plasma and tissue concentration may either be increased (e.g. cyclosporin, theophylline, corticosteroids) or decreased (e.g., lamotrigine).

It is not known if there are interactions between oral contraceptives and isotretinoin or topical acne agents.

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

4.6 Fertility, pregnancy and lactation

Effects on Fertility

No data available.

Use in Pregnancy

Category B3.

Pregnancy must be excluded before starting LOETTE. If pregnancy occurs during use of LOETTE, the preparation must be withdrawn immediately.

Oral contraceptives have not been shown to have any deleterious effects on the fetus or to increase the incidence of miscarriage in women who discontinue their use prior to conception.

Studies do not suggest a teratogenic effect when oral contraceptives are taken inadvertently during early pregnancy.

Animal studies have shown that high doses of progestogens can cause masculinisation of the female fetus. The results of these experiments in animals do not seem to be relevant to humans because of the low doses used in oral contraceptives.

Use in Lactation

Estrogen-containing oral contraceptives given in the post-partum period may interfere with lactation. There may be a decrease in the quantity and a change in the composition of the breast milk. Furthermore, small amounts of contraceptive steroids and/or metabolites have been identified in the milk of mothers receiving them. A few adverse effects on the child have been reported, including jaundice and breast enlargement. The use of estrogen-containing oral contraceptives should be deferred until the infant has been completely weaned.

4.7 Effect 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)

Use of combined oral contraceptives has been associated with increased risk of the following:

Arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, venous thrombosis, transient ischemic attack and pulmonary embolism.

Cervical intraepithelial neoplasia and cervical cancer.

Breast cancer diagnosis.

Benign hepatic tumours (e.g. focal nodular hyperplasia, hepatic adenomas).

Other adverse reactions, per CIOMS frequency categories, are listed below:

Very Common:	≥10%
Common:	≥1% and <10%
Uncommon:	≥0.1% and <1%
Rare:	≥0.01% and <0.1%
Very Rare:	<0.01%.

Adverse Reactions by Body System

Infections and Infestations

Common	Vaginitis, including candidiasis.

Neoplasms benign, malignant, and unspecified

Very Rare	Hepatic adenomas, hepatocellular carcinomas.

Vascular Disorders

Very Rare	Aggravation of varicose veins.

Gastro-intestinal Disorders

Common	Nausea, vomiting, abdominal pain
Uncommon	Abdominal cramps, bloating
Very Rare	Pancreatitis; ischaemic colitis
Unknown	Inflammatory bowel disease (Crohn's disease, ulcerative colitis).

Hepato-biliary Disorders

Rare	Cholestatic jaundice
Very Rare	Gallbladder disease, including gallstones*
Unknown	Hepatocellular injury (e.g. hepatitis, hepatic function abnormal).

Metabolism and Nutrition Disorders

Uncommon	Changes in appetite (increase or decrease)
Rare	Glucose intolerance
Very Rare	Exacerbation of porphyria.

Psychiatric Disorders

Common	Mood changes, including depression, changes in libido.

Nervous Disorders

Very Common	Headache, including migraines
Common	Nervousness, dizziness
Very Rare	Exacerbation of chorea.

Skin and Subcutaneous Tissue Disorders

Common	Acne
Uncommon	Rash, chloasma (melasma), which may persist, hirsutism, alopecia
Rare	Erythema nodosum
Very Rare	Erythema multiforme.

Eye Disorders

Rare	Intolerance to contact lenses
Very Rare	Optic neuritis**, retinal vascular thrombosis.

Reproductive System and Breast Disorders

Very Common	Metrorrhagia (breakthrough bleeding/spotting)
Common	Breast pain, tenderness, enlargement, secretion, dysmenorrhoea, change in menstrual flow, change in cervical ectropian and secretion, amenorrhoea.

Renal and Urinary Disorders

Very Rare	Haemolytic uraemic syndrome.

Immune System Disorders

Rare	Anaphylactic/anaphylactoid reactions including very rare cases of urticaria, angioedema and severe reactions with respiratory and circulatory symptoms
Very Rare	Exacerbation of systemic lupus erythematosus.

General Disorders and Administration Site Conditions

Common	Fluid retention/oedema.

Investigations

Common	Changes in weight (increase or decrease)
Uncommon	Increase in blood pressure, changes in serum lipid levels, including hypertriglyceridaemia

Rare	Decrease in serum folate levels***.

* Oral contraceptives may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.

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

*** Serum folate levels may be depressed by oral contraceptive therapy.

The most serious adverse reactions associated with the use of oral contraceptives are indicated under section 4.3, Contraindications and section 4.4, Special Warnings and Precautions for Use).

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

Signs and Symptoms

Symptoms of oral contraceptive overdose in adults and children may include nausea, vomiting breast tenderness, dizziness, abdominal pain, drowsiness/fatigue; withdrawal bleeding may occur in females. In children, serious ill effects have not been reported following large doses of oral contraceptives.

Recommended Treatment

Treatment of overdose, if necessary, is directed to the symptoms.

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

Oral Contraception

The contraceptive effects of the hormonal components contained in LOETTE are based on the inhibition of ovulation (by suppression of gonadotropin release) and are believed to include changes in the cervical mucus, which increase the difficulty of sperm penetration into the uterus. Additionally, changes could be expected in the endometrium that may reduce the likelihood of implantation.

Acne

Acne treatment with LOETTE is based on estrogen-induced increases in sex hormone binding globulin (SHBG). Because testosterone binds to SHBG, bioavailable testosterone is reduced. In addition, LOETTE suppresses gonadotropin production, leading to decreased ovarian production of androgens, including androstenedione. Serum levels of 3 a-androstenediol glucuronide (a marker of peripheral 5 a-reductase activity) are also reduced. These biochemical changes produced by the co-administration of levonorgestrel and ethinyl oestradiol are associated with improvement of acne in otherwise healthy women.

Clinical Trials

Contraception

An ongoing open-label, non-comparative multi-centre phase III clinical study was conducted in 1,447 women receiving LOETTE for a planned individual maximum of 36 cycles. Six cycles were completed by 789 women. Of 7,720 cycles of exposure that were evaluated for efficacy, a total of 5 pregnancies were reported. This represents an overall user-efficacy (typical user-efficacy) pregnancy rate of 0.84 per 100 woman-years (over 99% effective at preventing pregnancy). This rate includes patients who missed up to 5 non-consecutive pills per cycle or up to 3 consecutive pills per cycle.

The overall user-efficacy pregnancy rates for LOETTE and other forms of contraception from a number of non-comparative trials based on historical data are given below:

Oral Contraceptive	Overall user-efficacy (Pearl Index)	Effectiveness* at Preventing Pregnancy
LOETTE 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 levonorgestrel	0.30 –3.0	97.00% - 99.7%

* 100% - (Pearl Index) = User effectiveness per 100-woman 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 LOETTE is 99.16%, compared historically with the contraceptive efficacy of 99.7% for 150μg levonorgestrel/30μg ethinylestradiol tablets, this represents a 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 7,508 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 LOETTE 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 the table below.

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 Loette (6 cycle)	1447	7508	4.3	12.1	2.6	26 - 30	4.8
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 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 7 days in 86% of cycles (mean 4.8 days), and the mean intensity was light for the most common episode length (4 to 6 days). The mean cycle length, excluding cycle 1, was 29.1 days, and 90% of the cycles ranged in duration from 26 to 30 days. The cycle control for LOETTE remains consistent with these values over time.

Acne

Two (2) randomised, double blind, placebo-controlled, 6-cycle, multicentre, phase III clinical studies were done to evaluate the efficacy and safety of levonorgestrel/ethinylestradiol (LNG/EE) 100μg/20μg for the treatment of moderate acne. Study 1 was conducted at 12 sites in the United States and at 1 site each in Canada and Australia, and study 2 was conducted at 18 sites in the United States. Patients in studies 1 and 2 were randomly assigned to receive 28-day packs of either LNG/EE or placebo tablets. Those in the LNG/EE group received active tablets for 21 consecutive days and inert tablets for the subsequent 7 days. The study medication was taken for up to 6 cycles during the studies. Moderate acne was defined in the clinical trials as a total facial count of 6-200 non-inflammatory lesions (comedones), 10-75 inflammatory lesions (papules and pustules) and 0-5 nodules.

In both studies, LNG/EE treatment consistently produced greater mean reductions in lesion counts than placebo treatment. Generally, the differences between treatment groups became apparent at cycles 2 or 3 and increased over time, becoming significant at cycles 4, 5 or 6. The combined clinical global assessment results showed that a significantly greater percentage of patients in the LNG/EE treatment group than in the placebo group rated clear or mild at end-of-study (EOS).

Mean percentage changes in the total inflammatory, total non-inflammatory, total lesion counts and clinical global assessment (mild or clear) at EOS compared with baseline for each individual study, as well as pooled data, are shown in the table below.

Analysis of Inflammatory, Non-inflammatory, Total Lesion Counts and Clinical Global Assessment from Baseline to End-Of-Study (EOS)

Parameter	Time	LNG/EE	Placebo	Difference p-value[1]
Study 1		n = 174	n = 176	
Inflammatory Lesion Count	Baseline End-of-study (EOS) Change	20±11 12±10 -33%	20±15 15±24 -25%	0.11
Non-inflammatory Lesion Count	Baseline End-of-study Change	51±67 30±28 -21%	43±42 32±27 -13%	0.16
Total Lesion Count	Baseline End-of-study Change	71±70 42±32 -30%	63±52 46±38 -20%	0.02*
Clinical Global Assessment – mild or clear	Baseline End-of-study	12% 47%	8.3% 42%	0.25
Study 2		n = 185	n = 186	
Inflammatory Lesion Count	Baseline End-of-study Change	22±12 14±12 -32%	22±11 16±14 -22%	0.04*
Non-inflammatory Lesion Count	Baseline End-of-study Change	50±52 44±67 -13%	47±43 49±67 +4%	0.05*

Total Lesion Count	Baseline End-of-study Change	72±56 44±67 -23%	69±47 65±72 -9%	0.02*
Clinical Global Assessment – mild or clear	Baseline End-of-study	11% 48%	12% 38%	0.02*
Pooled		n = 359	n = 362	
Inflammatory Lesion Count	Baseline End-of-study Change	21±11 13±11 -32%	21±13 15±20 -24%	0.01*
Non-inflammatory Lesion Count	Baseline End-of-study Change	51±60 37±53 -17%	45±43 41±53 -4%	0.02*
Total Lesion Count	Baseline End-of-study Change	72±63 50±58 -26%	66±50 56±59 -14%	0.001*
Clinical Global Assessment – mild or clear	Baseline End-of-study Change	11% 48%	10% 40%	0.01*

*significant

[1] = Between-group difference based on mean change adjusted for baseline, study centre, antibiotic use and weight.

*EOS uses the last observation point for each patient. For patients who withdrew from the study before taking study medication, the baseline value was used in the analysis.

Furthermore, there was no statistically significant difference between measured mean weight gain from baseline to end of study (up to 6 cycles) in women treated with LNG/EE (0.72 ± 2.64 kg) and women treated with placebo (0.51 ± 2.77 kg).

5.2 Pharmacokinetic properties

Absorption

No specific investigation of the absolute bioavailability of LOETTE in humans has been conducted. However, literature indicates that levonorgestrel is rapidly and completely absorbed after oral sugar coated tablet administration (bioavailability about 100%) and is not subject to first-pass metabolism. Ethinylestradiol is rapidly and almost completely absorbed from the gastrointestinal tract but due to first-pass metabolism in gut mucosa and liver, the bioavailability of ethinylestradiol is between 38% and 48%, with marked inter-individual variation.

After a single dose of LOETTE to 22 women under fasting conditions, maximum serum concentrations of levonorgestrel are 2.8 ± 0.9 ng/mL (mean ± SD) at 1.6 ± 0.9 hours. At steady state, attained from day 19 onwards, maximum levonorgestrel concentrations of 6.0 ± 2.7 ng/mL are reached at 1.5 ± 0.5 hours after the daily dose. The minimum serum levels of levonorgestrel at steady state are 1.9 ± 1.0 ng/mL. Observed levonorgestrel concentrations increased from day 1 (single dose) to days 6 and 21 (multiple doses) by 34% and 96%, respectively. Unbound levonorgestrel concentrations increased from day 1 to days 6 and 21 by 25% and 83%, respectively. The kinetics of total levonorgestrel are nonlinear due to an increase in binding of levonorgestrel to sex hormone binding globulin (SHBG), which is attributed to increased SHBG levels that are induced by the daily administration of ethinylestradiol.

Following a single dose, maximum serum concentrations of ethinylestradiol of 62 ± 21 pg/mL are reached at 1.5 ± 0.5 hours. At steady state, attained from at least day 6 onwards, maximum concentrations of ethinylestradiol were 77 ± 30 pg/mL and were reached at 1.3 ± 0.7 hours after the daily dose. The minimum serum levels of ethinylestradiol at steady state are 10.5 ± 5.1 pg/mL. Ethinylestradiol concentrations did not increase from days 1 to 6, but did increase by 19% from days 1 to 21.

Distribution

Levonorgestrel in serum is primarily bound to SHBG. Ethinylestradiol is about 97% bound to plasma albumin. Ethinylestradiol does not bind to SHBG, but induces SHBG synthesis.

Metabolism

Levonorgestrel: 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.

Ethinylestradiol: 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 Cytochrome P450 (CYP3A4) vary widely among individuals and may explain the variation in rates of ethinylestradiol 2-hydroxylation. Ethinylestradiol is excreted in the urine and faeces as glucuronide and sulfate conjugates, and undergoes enterohepatic circulation.

Elimination

The elimination half-life for levonorgestrel is approximately 36 ± 13 hours at steady state. Levonorgestrel and its metabolites are primarily excreted in the urine (40% to 68%) and about 16% to 48% are excreted in faeces. The elimination half-life of ethinylestradiol is 18 ± 4.7 hours at steady state.

5.3 Preclinical safety data

Genotoxicity

There is some evidence 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 does not appear to be genotoxic.

Carcinogenicity

Long term continuous administration of natural or 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 benign mammary tumours, although a similar effect was not observed 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. It must be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours (see section 4.4, Special Warnings and Precautions for Use, Carcinoma of the Reproductive Organs and Hepatic Neoplasia/Liver Disease).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pink active tablet:

Microcrystalline cellulose,
Lactose monohydrate,
Polacrilin potassium,
Magnesium stearate,
Macrogol 1500,
Hypromellose,
Titanium dioxide,
Iron Oxide Red.

White inactive tablet:

Lactose monohydrate,
Maize starch

Magnesium stearate,
Macrogol 1500,
Macrogol 400,
Hypromellose,
Hyprolose,
Titanium dioxide.

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.

Protect from light.

6.5 Nature and contents of container

LOETTE tablets are presented in PVC/aluminium blister. The blistered product is placed in an aluminium pouch with a silica gel desiccant.

One, two#, three and four# month packs contain 1, 2, 3 and 4 blisters respectively.

not currently available.

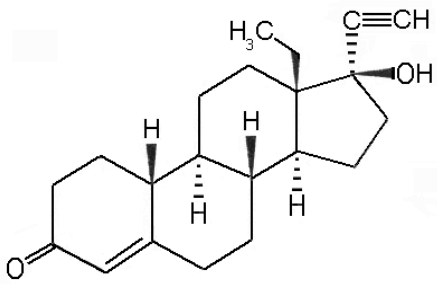
6.6 Special precautions for disposal

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

6.7 Physicochemical properties

Chemical structure

Levonorgestrel

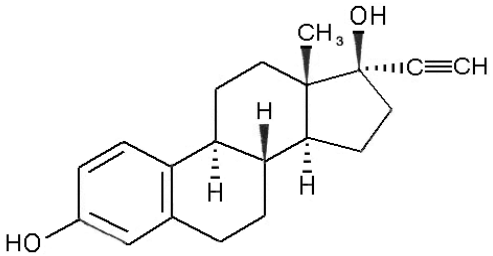


Chemical Formula: $C_{21}H_{28}O_2$
Molecular Weight: 312.45
Melting Point: 232-239°C

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

Levonorgestrel is a white, odourless crystalline powder. It is practically insoluble in water, slightly soluble in alcohol, acetone, ether, and soluble in chloroform.

Ethinylestradiol



Chemical Formula: $C_{20}H_{24}O_2$
Molecular Weight: 296.41
Melting Point: 181-185°C

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

Ethinylestradiol is a white to creamy white, odourless, crystalline powder. It is insoluble in water and soluble in alcohol, chloroform, ether, vegetable oils, and aqueous solutions of alkali hydroxides.

CAS number

Levonorgestrel: 797-63-7
Ethinylestradiol: 57-63-6

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

12 October 1998

10. DATE OF REVISION

6 December 2019

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
3	Editorial
8	Sponsor details updated