NEW ZEALAND DATA SHEET

1. PRODUCT NAME

LOETTE® 20 µg and 100 µg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 µg Ethinylestradiol and 100 µg Levonorgestrel

Excipients with known effects:

- Lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Each LOETTE calendar blister pack contains 21 pink active tablets and 7 white inactive tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LOETTE is indicated for the prevention of pregnancy.

4.2 Dose and method of administration

How to Take LOETTE

To achieve maximum contraceptive effectiveness, LOETTE must be administered as directed and at the same time every day, at intervals not exceeding 24 hours.

How to Start LOETTE

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

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 from the first day of therapy if the tablets are begun on Day 1 as described. Starting on Days 2-7 is allowed, but during the first cycle 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 discontinuance of the pink active tablet, the woman should use a back-up non-hormonal 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 **Advice in Case of Vomiting or Diarrhoea** and section 4.5) 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 (COC)

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 of 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 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 for 7 consecutive days.

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 pills 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 pills 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 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 for the 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 period (see section 4.4, Venous Thrombosis and Thromboembolism, and section 4.6).

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 tablet 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 active tablet taking days.

If the user 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.

Advice in Case of 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 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.

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.

Use in the Elderly

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

4.3 Contraindications

LOETTE is contraindicated in patients with:

- A history of, or current deep vein thrombosis, thrombophlebitis or thromboembolic disorders; thrombogenic valvulopathies or thrombogenic rhythm disorders.
- Hereditary or acquired predisposition for venous or arterial thrombosis.
- Cerebrovascular or coronary artery disease.
- Hereditary or acquired thrombophilias.
- Hepatic adenomas or carcinomas, cholestatic jaundice of pregnancy, jaundice with prior combined oral contraceptive use or active liver disease, as long as liver function has not returned to normal.
- Known or suspected carcinoma of the breast or other known or suspected estrogen-dependent neoplasias.
- Diabetes with vascular involvement.
- Headaches with focal neurological symptoms (such as aura) including hemiplegic migraine.
- Uncontrolled hypertension.
- Undiagnosed vaginal bleeding.
- Pancreatitis associated with severe hypertriglyceridaemia (current or history).
- Known or suspected pregnancy.
- COCs 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, Hepatitis C).

- 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.

Cigarette Smoking

Cigarette smoking increases the risk of serious cardiovascular side effects (e.g. myocardial infarction, stroke) from oral-contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

Thromboembolic Disorders

Use of combined oral contraceptives is associated with an increased risk of venous and arterial thrombotic and thromboembolic events.

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.

New users of combined oral contraceptives should be started on preparations containing less than 50 micrograms of estrogen.

Arterial Thrombosis and Thromboembolism

The use of combined oral contraceptives increases the risk of arterial thrombotic and thromboembolic events. Reported events include myocardial infarction and cerebrovascular events (ischaemic and haemorrhagic stroke, transient ischemic attack). The risk of arterial thrombotic and thromboembolic events is further increased in women with underlying risk factors or predisposing conditions such as cigarette smoking, hypertension, hyperlipidaemias, obesity, diabetes, pre-eclamptic toxaemia and increasing age. Caution must be exercised when prescribing LOETTE for women with risk factors or predisposing conditions for arterial thrombotic or thromboembolic events. COC users with migraine (particularly migraine with aura) may be at increased risk of stroke.

Venous Thrombosis and Thromboembolism

The use of combined oral contraceptives increases the risk of venous thrombotic and thromboembolic events. Use of any combined oral contraceptives increases the risk of venous thrombotic and thromboembolic events compared to no use. The excess risk is highest during the first year a woman ever uses a combined oral contraceptive. Venous thromboembolism (VTE) manifesting as deep venous thrombosis and/or pulmonary embolism may occur during the use of all combined oral contraceptives. The approximate incidence of VTE in users of low estrogen dose (< 50 μg ethinylestradiol) oral contraceptives is up to 4 per 10,000 woman- years compared to 0.5-3 per 10,000 woman-years in non-oral contraceptive users. The increased risk of venous thrombotic and thromboembolic events during any combined oral contraceptive use is less than

the incidence associated with pregnancy (which is estimated as 6 per 10,000 pregnant woman-years). Venous thromboembolism is fatal in 1-2% of cases.

The risk of venous thrombotic and thromboembolic events is further increased in women with conditions predisposing for venous thrombosis and venous thromboembolism. Examples of predisposing conditions are: obesity, surgery or trauma with increased risk of thrombosis, recent delivery or second-trimester abortion, prolonged immobilisation and increasing age.

A two- to four-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of combined oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, combined oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery with an increased risk of thrombosis, and during prolonged immobilisation.

Because the immediate post-partum period is associated with an increased risk of thromboembolism, combined oral contraceptive use should begin no sooner than the 28th postpartum day following either delivery in a non-lactating woman or second-trimester abortion.

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).

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

Hepatitis C

During clinical trials with the combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with and without ribavirin, transient, asymptomatic elevations of alanine transaminase (ALT) greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medications such as combined oral contraceptives.

LOETTE must be discontinued 2 weeks prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin. LOETTE can be restarted approximately 2 weeks following completion of treatment with the combination drug regimen (see section 4.3).

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

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal.

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. Because of these demonstrated effects, diabetic women and women with impaired glucose tolerance should be carefully observed while taking oral contraceptives. See section 4.3.

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 an oral contraceptive.

Women who are being treated for hyperlipidaemias should be followed closely if they elect to use combined oral contraceptives.

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; and if 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 (see section 4.3).

Migraine/Headache

The onset or exacerbation of migraine or development of headache with a new pattern that is recurrent, persistent or severe requires discontinuation of combined oral contraceptives and evaluation of the cause.

Women with migraine (particularly migraine with aura) who take combined oral contraceptives may be at increased risk of stroke (see section 4.4, Arterial Thrombosis and Thromboembolism).

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 has been excluded.

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

Medical Examinations

A complete personal and family medical history and physical examination should be taken prior to the initiation of LOETTE use, and should be repeated at least annually during the use of LOETTE. Special attention should be given to blood pressure, breasts, abdomen and pelvic organs. A Papanicolaou smear and relevant laboratory tests should be carried out.

Patients with Epilepsy

LOETTE should be used with caution in patients with epilepsy. The deterioration of this condition may indicate that LOETTE should be discontinued (see also section 4.5).

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 medicine related. Women with a history of depression should be carefully observed and the medicine discontinued if depression recurs to a serious degree.

HIV Infection

LOETTE does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Vomiting and/or Diarrhoea

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

4.5 Interaction with other medicines and other forms of interaction

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 and section 4.4, 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, and substances that induce hepatic microsomal enzymes, such as rifampicin, phenytoin, 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.

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, such as rifampicin, resulting in decreased ethinylestradiol serum concentrations. 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, e.g. ascorbic acid

(vitamin C) and paracetamol, and substances that inhibit cytochrome P450 3A4 isoenzymes, (e.g. itraconazole, fluconazole, and indinavir).

Ethinylestradiol may inactivate certain CYP450 enzymes and therefore may 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).

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

Effect 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.

4.6 Fertility, pregnancy and lactation

Pregnancy - Category B3.

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

Extensive epidemiological studies have revealed no increased risk of birth defects in children born to women who used combined oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect; particularly in so far as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy. See also section 4.3.

Lactation

Estrogen-containing oral contraceptives given in the post-partum period may affect 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 Effects on ability to drive and use machines

LOETTE is presumed to be safe or unlikely to produce an effect on the ability to drive or use machines.

4.8 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

Not known	Inflammatory bowel disease (Crohn's disease, ulcerative colitis).

Hepato-biliary disorders

Rare	Cholestatic jaundice
Very Rare	Gallbladder disease, including gallstones*
Not known	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 ectropion 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.

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

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.

Treatment

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

LOETTE is a combined oral contraceptive tablet containing the synthetic progestogen, levonorgestrel, and the synthetic estrogen, ethinylestradiol.

The hormonal components of LOETTE suppress gonadotropins in a manner that inhibits ovulation, which leads to contraception.

Non Contraceptive Benefits

The following non-contraceptive health benefits related to the use of combination oral contraceptives are supported by epidemiological studies, which largely utilised oral contraceptive formulations containing doses exceeding 0.035 mg of ethinylestradiol or 0.05mg mestranol.

1. Effects on menses

   Increased menstrual cycle regularity.

   Decreased blood loss and decreased incidence of iron deficiency anaemia.

   Decreased incidence of dysmenorrhoea.

2. Effects related to inhibition of ovulation

   Decreased incidence of ectopic pregnancies.

   Decreased incidence of functional ovarian cysts.

3. Effects from long-term use

   Decreased incidence and severity of acne.

   Decreased incidence of fibroadenomas and fibrocystic disease of the breast.

   Decreased incidence of acute pelvic inflammatory disease.

   Decreased incidence of endometrial carcinoma.

   Decreased incidence of ovarian carcinoma.

Clinical Trials

An open-label multicentre phase III clinical study was conducted in 1,447 women receiving LOETTE. Of 7,720 cycles of exposure evaluable 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). This rate includes patients who did not take the medicine correctly.

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 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%.

Distribution

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. Levonorgestrel in serum is primarily bound to SHBG.

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 accumulated by 19% from days 1 to 21. Ethinylestradiol is about 97% bound to plasma albumin. Ethinylestradiol does not bind to SHBG, but induces SHBG synthesis.

Metabolism

Levonorgestrel: The most important metabolic pathway occurs in the reduction of the Δ4-3-oxo group and hydroxylation at positions 2α, 1β, and 16β, followed by conjugation. Most of the metabolites that circulate in the blood are sulfates of 3α, 5β-tetrahydro-levonorgestrel, while excretion occurs predominantly in the form of glucuronides. Some of the parent levonorgestrel also circulates as 17β-sulfate. Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for the wide variation observed in levonorgestrel concentrations among users.

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 (CYP3A) vary widely among individuals and can 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

No effects that might indicate an unexpected risk to humans were observed during systemic tolerance studies after repeated administration of combined oral contraceptives.

Carcinogenesis

Long-term repeated dose toxicity studies for evaluation of a possible tumourigenic activity did not indicate a tumourigenic potential in case of therapeutic use of the preparation in humans. However, it must be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

Mutagenesis

In vitro and *in vivo* studies performed with ethinylestradiol and levonorgestrel gave no indication of a mutagenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each pink active tablet contains 100 µg levonorgestrel and 20 µg ethinylestradiol and the excipients: microcrystalline cellulose, lactose monohydrate, polacrilin potassium, magnesium stearate, macrogol 1450, glycol montanate and Opadry YS-1-14587-A Pale Pink.

Each white inactive tablet contains lactose monohydrate, microcrystalline cellulose, magnesium stearate, polacrilin potassium, macrogol 1500, glycol montanate and Opadry Y-5-18024-A White (US version).

6.2 Incompatibilities

None stated.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 25ºC.

6.5 Nature and contents of container

One-month pack containing one blister tray or a three-month pack containing 3 blister trays. Each blister tray contains 21 pink active tablets, each containing levonorgestrel 100 µg and ethinylestradiol 20 µg, and 7 white inactive tablets.

6.6 Special precautions for disposal and other handling

None stated.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand, 1140

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

13 August 1998

10. DATE OF REVISION OF THE TEXT

19 November 2018

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
5.1	Clarification of the mode of action