

LOETTE® 21

1. DESCRIPTION

1.1 Active ingredients, active moieties

Levonorgestrel 100 µg; ethinylestradiol 20 µg

1.2 Representative trade names

Loette® 21 Tablets

1.3 Pharmacological class, therapeutic class

Estrogen-progestin combination oral contraceptive (COC)

1.4 Dosage forms and intended routes of administration

Tablets for oral use

1.5 Composition and pharmaceutical characteristics

Loette 21 is a combined oral contraceptive (COC) tablet containing the synthetic progestin, levonorgestrel, and the synthetic estrogen, ethinylestradiol. Round, pink biconvex tablet with 'W' debossed on one side and '912' debossed on the other.

1.6 Physical characteristics

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

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

2. INDICATIONS

Loette 21 is indicated for the prevention of pregnancy.

Loette 21 is also indicated for the treatment of moderate acne vulgaris not controlled by conventional therapy (e.g. topical preparations and oral antibiotics) in postmenarchal, premenopausal women ≥14 years who accept contraception.

3. DOSAGE AND ADMINISTRATION

The recommended dose for the prevention of pregnancy and the treatment of acne is the same.

To achieve maximum contraceptive effectiveness, Loette 21 must be administered as directed and at the same time every day, preferably after the evening meal or at bedtime.

Do not initiate or continue the use of "Loette 21 " if pregnancy is known or suspected.

3.1 How to take "Loette 21"

Tablets 1-21 contain active ingredients (active tablets)

Tablets must be taken in the order directed on the package every day at about the same time. One tablet is to be taken daily for 21 consecutive days, followed by a 7-day tablet-free interval. Each subsequent pack is started on the day after the tablet-free interval. A withdrawal bleed usually starts on Days 2-3, after the last active tablet, and may not have finished before the next pack is started.

3.2 How to start "Loette 21"

- ***No hormonal contraceptive use within the preceding month***

The user should begin taking Loette 21 on Day 1 of her natural menstrual cycle (i.e., the first day of menstrual bleeding).

Beginning Loette 21 use on Days 2-7 of the menstrual cycle (e.g., Sunday start) is allowed; however, a nonhormonal back-up method of birth control (e.g., condoms, spermicide) is recommended during the first 7 days of Loette 21 use.

- ***Switching from another COC***

Preferably, Loette 21 use should begin the day after the last active tablet of the previous COC pack has been taken but no later than the day following the usual tablet-free or inactive tablet interval of the previous COC.

- ***Switching from a progestin-only method of birth control (pill, implant, intrauterine device [IUD], injection)***

- The user may discontinue use of a progestin-only pill on any day; use of Loette 21 should begin the following day.
- Loette 21 use should begin on the same day that a progestin-only implant or a progestin-only IUD is removed.
- Loette 21 use should begin on the day that the next progestin-only injection is scheduled.

In each of these situations, the user should be advised to use a nonhormonal back-up method of birth control during the first 7 days of Loette 21 use.

- ***Following first-trimester abortion***

Loette 21 use may begin immediately. Additional contraceptive measures are not needed.

- ***Postpartum***

Because the immediate postpartum period is associated with an increased risk of thromboembolism, Loette 21 use should begin no sooner than the 28th postpartum day following either delivery in a nonlactating woman or second-trimester abortion. The woman should be advised to use a nonhormonal back-up method of birth control during the first 7 days of Loette 21 use. However, if intercourse has already occurred, pregnancy must be ruled out before Loette 21 use is begun; otherwise, the woman must wait until her first menstrual period before beginning Loette 21 use. (See section 5.1 Venous and arterial thrombosis and thromboembolism and section 8 Lactation).

3.3 Management of missed tablets

Contraceptive protection may be reduced if active tablets are missed, particularly if the missing of tablets extends the tablet-free interval.

- If one active tablet is missed but is remembered within 12 hours of the usual dose, it should be taken as soon as it is remembered. Subsequent tablets should be taken at the usual time.
- If one active tablet is missed and is remembered more than 12 hours after the usual dose or if two or more active tablets are missed, contraceptive protection may be reduced. The last missed tablet should be taken as soon as it is remembered, which may result in the user taking two tablets on the same day. Subsequent tablets should be taken at the usual time. A nonhormonal back-up method of birth control must be used for the next 7 days.

For 21-day packs only: If the user takes the last active tablet before the 7-day interval during which use of a nonhormonal back-up method of birth control is required has ended, she must begin a new pack immediately; there should be no tablet-free interval between packs. This prevents an extended break in the tablet-taking interval, thereby reducing the risk of escape ovulation. The user is unlikely to have a withdrawal bleed until all tablets in the new pack are taken, although she may experience spotting or breakthrough bleeding on tablet-taking days. If the user does not have a withdrawal bleed after all tablets in the new pack are taken, pregnancy must be ruled out before tablet-taking is resumed.

- If one active tablet is missed, it should be taken as soon as it is remembered. Subsequent tablets should be taken at the usual time.
- If two consecutive active tablets are missed during Week 1 or Week 2, two tablets should be taken on both the day remembered and the following day. Subsequent tablets should be taken at the usual time. A nonhormonal back-up method of birth control must be used for the next 7 days.
- If two consecutive active tablets are missed during Week 3 or if three or more

consecutive active tablets are missed during Weeks 1-3, the following apply:

- Day 1 starters should discard any tablets remaining in the current pack and start a new pack the same day.
- Sunday starters should continue taking one tablet every day until the following Sunday. On Sunday, any tablets remaining in the current pack should be discarded, and a new pack should be started the same day.
- Both Day 1 and Sunday starters must use a nonhormonal back-up method of birth control for the next 7 days. The user may not have a withdrawal bleed until all tablets in the new pack have been taken. If the user does not have a withdrawal bleed after all tablets in the new pack have been taken, pregnancy must be ruled out before tablet-taking is resumed.

3.4 Advice in case of vomiting and/or diarrhea

If vomiting or diarrhea occurs within 4 hours after tablet-taking, tablet absorption may be incomplete. Use of tablets from a back-up pack is required, as outlined below. Refer to recommendations for **MANAGEMENT OF MISSED TABLETS** (see section 3.3 Management of missed tablets).

For Monophasic COCs: The user must take the needed active tablet(s) from a back-up pack.

3.5 How to delay a period

For Monophasic COCs: To delay a menstrual period, the user should skip the tablet-free interval and immediately begin a new pack of Loette 21. The delay may be continued for as long as desired up until all tablets in the new pack are taken. During the delay, the user may experience breakthrough bleeding or spotting. Regular intake of Loette 21 should be resumed after the usual 7 day tablet-free interval.

4. CONTRAINDICATIONS

Loette 21 must not be used in women with any of the following conditions:

1. Deep vein thrombosis (current or history).
2. Thromboembolism (current or history).
3. Cerebrovascular or coronary artery disease.
4. Thrombogenic valvulopathies
5. Thrombogenic rhythm disorders
6. Hereditary or acquired thrombophilias.
7. Headache with focal neurological symptoms, such as aura.
8. Diabetes with vascular involvement.
9. Uncontrolled hypertension.
10. Known or suspected carcinoma of the breast, or other known or suspected estrogen dependent neoplasia.
11. Hepatic adenomas or carcinomas, or active liver disease, as long as liver function has not returned to normal.

12. Undiagnosed vaginal bleeding.
13. Pancreatitis associated with severe hypertriglyceridemia (current or history).
14. Known or suspected pregnancy.
15. Hypersensitivity to any of the components of Loette 21.
16. Disorders of lipometabolism.
17. Sickle cell anemia.

Loette 21 is contraindicated for concomitant use with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir (see section 5 Special Warnings and section 11 Interactions).

REASONS FOR THE IMMEDIATE DISCONTINUATION OF LOETTE 21

1. Occurrence for the first time of migrainous headaches or the more frequent occurrence of unusually severe headaches.
2. Acute disturbances of vision, hearing, or speech.
3. First symptoms of thrombophlebitis or thromboembolism (e.g., unusual pain in or swelling of the legs, stabbing pain on breathing, or coughing for no apparent reason).
4. Feeling of pain or tightness in the chest.
5. Six weeks before planned operations or during prolonged periods of immobilization.
6. Development of jaundice (cholestasis), hepatitis, or generalized pruritus.
7. Increase in epileptic seizures.
8. Significant rise in blood pressure.
9. Onset of severe clinical depression.
10. Severe upper abdominal pain or liver enlargement.
11. Pregnancy.

5. SPECIAL WARNINGS

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 who use COCs should be strongly advised not to smoke.

5.1 Venous and arterial thrombosis and thromboembolism

Use of COCs is associated with an increased risk of venous and arterial thrombotic and thromboembolic events.

Minimizing exposure to estrogens and progestins is in keeping with good principles of therapeutics. For any particular estrogen/progestin combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestin that is compatible with a low failure rate and the needs of the individual patient.

New acceptors of COCs should be started on preparations containing less than 50 µg of estrogen.

Full recovery from these disorders does not always occur, and it should be realized that in a few cases they are fatal. *The physician should therefore be alert to the earliest manifestations of these disorders. Should any of these occur or be suspected, oral contraceptives should be discontinued immediately.*

- **Venous thrombosis and thromboembolism**

Use of COCs increases the risk of venous thrombotic and thromboembolic events. Reported events include deep venous thrombosis and pulmonary embolism. For information on retinal vascular thrombosis (see section 5.2 Ocular lesions).

The use of any COC carries an increased risk of venous thrombotic and thromboembolic events compared with no use. The excess risk is highest during the first year a woman ever uses a combined oral contraceptive. This increased risk is less than the risk of venous thrombotic and thromboembolic events associated with pregnancy which is estimated as 60 cases per 100,000 women-years. Venous thromboembolism is fatal in 1% to 2% of cases.

Epidemiological studies have shown that the incidence of venous thromboembolism in users of low-estrogen oral contraceptives (<50 mcg ethinyl estradiol) ranges from about 20 to 40 cases per 100,000 women-years; this risk estimate varies according to the progestin. This compares with 5 to 10 cases per 100,000 women-years for non-users.

For all COCs:

The risk of venous thrombotic and thromboembolic events is further increased in women with conditions predisposing for venous thrombosis and thromboembolism. Caution must be exercised when prescribing COCs for such women.

Examples of predisposing conditions for venous thrombosis and thromboembolism are:

- obesity
- surgery or trauma with increased risk of thrombosis
- recent delivery or second-trimester abortion
- prolonged immobilization
- increasing age

Further risk factors, which represent contraindications for the use of COCs, are listed in section 4 Contraindications.

The relative risk of postoperative thromboembolic complications has been reported to be increased two- to four-fold with the use of COCs. The relative risk of venous thrombosis in women with predisposing conditions is twice that of women without such conditions. If feasible, COCs should be discontinued:

- for four weeks prior to and for two weeks after elective surgery with increased risk of thrombosis, and

- during prolonged immobilization.

Because the immediate postpartum period is associated with an increased risk of thromboembolism, COC use should begin no sooner than the 28th postpartum day following either delivery in a nonlactating woman or second-trimester abortion.

- **Arterial thrombosis and thromboembolism**

The use of COCs increases the risk of arterial thrombotic and thromboembolic events. Reported events include myocardial infarction and cerebrovascular events (ischemic and hemorrhagic stroke, transient ischemic attack). For information on retinal vascular thrombosis (see section 5.2 Ocular lesions).

The risk of arterial thrombotic and thromboembolic events is further increased in women with underlying risk factors.

Caution must be exercised when prescribing COCs for women with risk factors for arterial thrombotic and thromboembolic events.

Examples of risk factors for arterial thrombotic and thromboembolic events:

- smoking
- hypertension
- hyperlipidemias
- obesity
- increasing age

COC users with migraine (particularly migraine with aura) may be at increased risk of stroke (see section 4 Contraindications).

Further risk factors that represent contraindications for the use of COCs are listed in section 4.

THE RISK OF ARTERIAL THROMBOSES (E.G., STROKE, MYOCARDIAL INFARCTION) ASSOCIATED WITH COMBINED ORAL CONTRACEPTIVES INCREASES WITH AGE AND WITH HEAVY SMOKING. FOR THIS REASON, WOMEN OVER 35 YEARS OF AGE WHO USE ORAL CONTRACEPTIVES SHOULD BE STRONGLY ADVISED NOT TO SMOKE.

5.2 Ocular lesions

With use of COCs, there have been reports of retinal vascular thrombosis, which may lead to partial or complete loss of vision. If there are signs or symptoms such as visual changes, onset of proptosis or diplopia, papilledema, or retinal vascular lesions, the COC should be discontinued and the cause immediately evaluated.

5.3 Blood pressure

Increases in blood pressure have been reported in women taking COCs.

In women with hypertension or a history of hypertension or hypertension-related diseases (including certain renal diseases), another method of birth control may be preferable. If COCs are used in such cases, close monitoring is recommended; if a significant increase in blood pressure occurs, COCs should be discontinued.

Elevated blood pressure associated with COC use will generally return to baseline after stopping COCs, and there appears to be no difference in the occurrence of hypertension among ever- and never- users.

COC use is contraindicated in women with uncontrolled hypertension (see section 4 Contraindications).

5.4 Carcinoma of the reproductive organs

5.4.1 Cervical cancer

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

Some studies suggest that COC use may be associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women. For example, the results of one meta-analysis of 24 epidemiological studies indicated that among current users of oral contraceptives, the relative risk of invasive cervical cancer increased with increasing duration of use. The relative risk for 5 or more years' use versus never-use was 1.90 (95% confidence interval 1.69-2.13). The relative risk declined after use ceased and by 10 or more years was not significantly different from that in never-users. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors. In cases of undiagnosed abnormal genital bleeding, adequate diagnostic measures are indicated.

5.4.2 Breast cancer

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

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (1.24) of having breast cancer diagnosed in women who are using COCs compared to never-users. The increased risk gradually disappears during the course of the 10 years after cessation of COC use. These studies do not provide evidence for causation. The observed pattern of increased risk of breast cancer diagnosis may be due to earlier detection of breast cancer in COC users (due to more regular clinical monitoring), the biological effects of COCs, 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 COC 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.

5.5 Hepatic neoplasia/liver disease/hepatitis C

In very rare cases, hepatic adenomas, and in extremely rare cases, hepatocellular carcinoma may be associated with COC use. The risk appears to increase with duration of COC use. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

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 COC 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 COC, use a non-hormonal form of birth control, and consult their doctor.

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until liver function has returned to normal.

ALT elevations

During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir with/without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). Patients who are taking ethinylestradiol-containing medicinal products must switch to an alternative method of contraception (e.g. progestin only contraception or non-hormonal methods) prior to initiating ombitasvir / paritaprevir/ ritonavir and dasabuvir therapy (see section 4 Contraindications and section 11 Interactions).

5.6 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 COCs and evaluation of the cause.

Women with migraine (particularly migraine with aura) who take COCs may be at increased risk of stroke (see section 4 Contraindications).

5.7 Immune

• Angioedema

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

5.8 Gallbladder disease

Earlier studies reported an increased risk of surgically confirmed gallbladder disease in users of estrogens and oral contraceptives. However, more recent studies have shown that the relative risk of developing gallbladder disease may be minimal.

6. PRECAUTIONS

6.1. Medical examinations

Before COC use is initiated, a thorough individual history, family history, and physical examination, including a blood pressure determination, should be performed. An examination of the breasts, liver, extremities, and pelvic organs should also be conducted. A Papanicolaou (Pap) smear should be performed if the patient has been sexually active or if it is otherwise indicated.

Such medical examinations should be repeated at least annually during the use of COCs.

The first follow-up visit should occur 3 months after COCs are prescribed. At each annual visit, examination should include those procedures that were performed at the initial visit, as described previously.

The following conditions require strict medical supervision during the use of oral contraceptives. Deterioration of some of these conditions may indicate that the oral contraceptive should be discontinued: diabetes mellitus or a tendency towards diabetes mellitus, hypertension, varicose veins, a history of phlebitis, otosclerosis, multiple sclerosis, migraine, epilepsy, porphyria, tetany, chorea, renal dysfunction, systemic lupus erythematosus, obesity, family history of breast cancer and patient history of breast nodules, history of clinical depression, and conditions aggravated by fluid retention.

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.

Individual cases of intolerance to contact lenses have been reported in users of oral contraceptives. Contact lens wearers who develop changes in lens tolerance should be assessed by an ophthalmologist.

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

Vomiting or diarrhea may reduce the efficacy of oral contraceptives. During these gastrointestinal disturbances, tablet taking should be continued in order to avoid premature withdrawal bleeding. Also, additional nonhormonal methods of contraception (with the exception of the rhythm or temperature methods) should be used for the duration of the gastrointestinal disturbance and for 7 days following the upset. If the 7 days run beyond the end of the pack, the tablet-free interval is disregarded, and a new pack is started on the day following the intake of the last tablet in the previous pack. The user is unlikely to have a withdrawal bleed until the

end of the second pack, but she may experience spotting or breakthrough bleeding on 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 gastrointestinal disturbance is protracted, other methods of contraception should be considered.

In women receiving long-term therapy with hepatic enzyme inducers, another method of contraception should be advised (see section 11 Interactions).

Women receiving short courses of therapy with hepatic enzyme inducers or certain broad spectrum antibiotics should use additional nonhormonal methods of contraception (with the exception of the rhythm or temperature methods) in addition to regular intake of Loette 21 during the time of concomitant administration of interacting drugs (see section 11 Interactions). The additional contraception should continue during the intake of the concurrent medication and for 7 days after its discontinuation.

If these 7 days run beyond the end of the pack, the next pack should be started without a break. In this situation, a withdrawal bleed should not be expected until the end of the second pack. If the woman does not experience a withdrawal bleed at the end of the second pack, the possibility of pregnancy must be ruled out before resuming with the next pack.

With rifampicin, additional contraceptive precautions should be continued for 4 weeks after the drug's discontinuation, even if only a short course was administered.

6.2. Carbohydrate and lipid effects

Glucose intolerance has been reported in COC users. Women with impaired glucose tolerance or diabetes mellitus who use COCs should be carefully monitored. (See section 4 Contraindications).

A small proportion of women will have adverse lipid changes while taking OCs. Nonhormonal birth control should be considered in women with uncontrolled dyslipidemias. Persistent hypertriglyceridemia may occur in a small proportion of COC users.

Elevations of plasma triglycerides in COC 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 progestins may elevate low-density lipoprotein (LDL) levels and may render the control of hyperlipidemias more difficult. The net effect of a COC depends on the balance achieved between doses of estrogen and progestin and the nature and absolute amount of progestins used in the contraceptive. The amount of both hormones should be considered in the choice of a COC.

Women who are being treated for hyperlipidemias should be followed closely if they elect to use COCs.

6.3 Genital bleeding

In some women withdrawal bleeding may not occur during the tablet-free interval. If the COC 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 nonhormonal back-up method of birth control should be used until the possibility of pregnancy is excluded.

Breakthrough bleeding/spotting may occur in women taking COCs, especially during the first three months of use. The type and dose of progestin may be important. If this bleeding persists or recurs, nonhormonal causes should be considered and adequate diagnostic measures may be indicated to rule out pregnancy, infection, malignancy, or other conditions. If pathology has been excluded, continued use of the COC or a change to another formulation may solve the problem.

Some women may encounter post-pill amenorrhea (possibly with anovulation) or oligomenorrhea, especially when such a condition was preexistent.

6.4 Depression

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

6.5 Other

Patients should be counseled that this product does not protect against HIV infection (AIDS) or other sexually transmitted diseases.

Diarrhea and/or vomiting may reduce hormone absorption resulting in decreased serum concentrations (see section 3.4 Advise in case of vomiting and/or diarrhea and section 11 Interactions).

7. PREGNANCY

If pregnancy occurs during treatment with COCs, further intake should be discontinued. There is no conclusive evidence that the estrogen and progestin contained in the COC will damage the developing child if conception accidentally occurs during COC use. (See also Contraindications).

8. LACTATION

Small amounts of contraceptive steroids and/or metabolites have been identified in the milk of nursing mothers and a few adverse effects on the child have been

reported, including jaundice and breast enlargement. Lactation may be affected by COCs, as COCs may reduce the quantity and change the composition of breast milk.

The use of COCs is generally not recommended until the nursing mother has completely weaned her child.

9. PEDIATRIC USE

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

10. GERIATRIC USE

COCs are not indicated for use in postmenopausal women.

11. INTERACTIONS

Interactions between ethinyl estradiol (EE) and other substances may lead to decreased or increased serum EE 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 Contraindications and section 5 Special Warnings, 5.5 Hepatic neoplasia/liver disease/hepatitis C). Therefore, users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with this combination drug regimen. Loette 21 can be restarted 2 weeks following completion of treatment with this combination drug regimen.

Decreased EE serum concentrations may cause an increased incidence of breakthrough bleeding and menstrual irregularities and may possibly reduce efficacy of the COC.

During concomitant use of EE-containing products and substances that may lead to decreased EE serum concentrations, it is recommended that a nonhormonal back-up method of birth control (such as condoms and spermicide) be used in addition to the regular intake of Loette 21. In the case of prolonged use of such substances COCs should not be considered the primary contraceptive.

After discontinuation of substances that may lead to decreased EE serum concentrations, use of a nonhormonal back-up method is recommended for at least 7 days. Longer use of a back-up method is advisable after discontinuation of substances that have lead to induction of hepatic microsomal enzymes, resulting in decreased EE 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.

Examples of substances that may decrease serum EE concentrations:

- Any substance that reduces gastrointestinal transit time, and therefore, EE absorption.
- Substances that induce hepatic microsomal enzymes, such as rifampicin, rifabutin, barbiturates, primidone, phenylbutazone, phenytoin, dexamethasone, griseofulvin, topiramate, some protease inhibitors, modafinil.
- *Hypericum perforatum*, also known as St. John's Wort, and ritonavir* (possibly by induction of hepatic microsomal enzymes)

Examples of substances that may increase serum EE concentrations:

- Atorvastatin
- Competitive inhibitors for sulfation in the gastrointestinal wall, such as ascorbic acid (vitamin C) and paracetamol (acetaminophen)
- Substances that inhibit cytochrome P450 3A4 isoenzymes such as indinavir, fluconazole, and troleandomycin*

Troleandomycin may increase the risk of intrahepatic cholestasis during co-administration with COCs.

EE may interfere with the metabolism of other drugs by inhibiting hepatic microsomal enzymes, or by inducing hepatic drug conjugation, particularly glucuronidation. Accordingly, plasma and tissue concentrations may either be increased (e.g., cyclosporine, theophylline, corticosteroids) or decreased (e.g., lamotrigine).

In patients treated with flunarizine, use of oral contraceptives has been reported to increase the risk of galactorrhea.

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

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

* Although ritonavir is an inhibitor of cytochrome P450 3A4, treatment with ritonavir has been shown to decrease EE serum concentrations (see above).

12. INTERFERENCE WITH LABORATORY AND OTHER DIAGNOSTIC TESTS

Effects on laboratory parameters

The use of COCs may cause certain physiologic changes that may be reflected in 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.

13. EFFECTS ON ACTIVITIES REQUIRING CONCENTRATION AND PERFORMANCE

Not applicable

14. ADVERSE REACTIONS

Adverse reactions are listed in the Table per CIOMS frequency categories:

Very Common:	$\geq 10\%$
Common:	$\geq 1\%$ and $< 10\%$
Uncommon:	$\geq 0.1\%$ and $< 1\%$
Rare:	$\geq 0.01\%$ and $< 0.1\%$
Very Rare:	$< 0.01\%$

Use of COCs has been associated with increased risk of the following:

- Arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, transient ischemic attack, venous thrombosis and pulmonary embolism
- Cervical intraepithelial neoplasia and cervical cancer
- Breast cancer diagnosis
- Benign hepatic tumors (e.g., focal nodular hyperplasia, hepatic adenomas)

See also sections 5 Special warnings and 6 Precautions.

System Organ Class	Adverse Reaction
Infections and Infestations	
Common	Vaginitis, including candidiasis
Neoplasms benign, malignant, and unspecified	
Very Rare	Hepatocellular carcinomas
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

System Organ Class**Adverse Reaction**

Other reactions of possible immunologic origin may be listed under other organ system subheadings.

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
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Nervous system disorders

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

Eye disorders

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

Vascular disorders

Very Rare	Aggravation of varicose veins
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Gastrointestinal disorders

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

Hepato-biliary disorder

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

Skin and subcutaneous tissue disorders

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

Renal and urinary disorders

Very Rare	Hemolytic uremic syndrome
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Reproductive system and breast disorders

Very common	Breakthrough bleeding/spotting
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System Organ Class**Adverse Reaction**

Common	Breast pain, tenderness, enlargement, secretion; dysmenorrhea; change in menstrual flow; change in cervical ectropion and secretion; amenorrhea
General disorders and administration site conditions	
Common	Fluid retention/edema
Investigations	
Common	Changes in weight (increase or decrease)
Uncommon	Increase in blood pressure; changes in serum lipid levels, including hypertriglyceridemia
Rare	Decrease in serum folate levels***

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

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

*** Serum folate levels may be depressed by COC therapy. This may be of clinical significance if the woman becomes pregnant shortly after discontinuing COCs.

In addition, the following adverse events have been reported in women receiving oral contraceptives and are believed to be drug-related:

Temporary infertility after discontinuation of treatment, diminution in lactation when given immediately postpartum, reduced tolerance to carbohydrates, change in corneal curvature (steepening).

There is evidence of an association between the following adverse reaction reports and the use of oral contraceptives, although additional confirmatory data are needed: Mesenteric thrombosis, retinal thrombosis.

The following adverse events have been reported in users of oral contraceptives, but an association has neither been confirmed nor totally refuted:

Congenital anomalies, premenstrual syndrome, cataracts, Budd-Chiari syndrome, colitis, cerebral-vascular disease with mitral valve prolapse, lupus-like syndromes.

15. OVERDOSE

Symptoms of oral contraceptive overdosage in adults and children may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue; withdrawal bleeding may occur in females. There is no specific antidote and further treatment of overdose, if necessary, is directed to the symptoms.

16. MODE OF ACTION

COCs suppress gonadotropins in a manner that inhibits ovulation, which leads to contraception.

17. PHARMACODYNAMICS, CLINICAL EFFICACY

When taken consistently and correctly, the probable failure rate of COCs is 0.1% per year; however, the failure rate during typical use is 5% per year for all types of oral contraceptives. The efficacy of most methods of contraception depends upon the reliability with which they are used. Method failure is more likely if COC tablets are missed.

The following noncontraceptive health benefits related to the use of COCs are supported by epidemiological studies that largely utilized COC formulations containing doses exceeding 35 µg of EE or 50 µg of mestranol.

Effects on menses

- Improved menstrual cycle regularity
- Decreased blood loss and decreased incidence of iron-deficiency anemia
- Decreased incidence of dysmenorrhea

Effects related to inhibition of ovulation

- Decreased incidence of functional ovarian cysts
- Decreased incidence of ectopic pregnancies

Other noncontraceptive health benefits

- Decreased incidence of fibroadenomas and fibrocystic disease of the breast
- Decreased incidence of acute pelvic inflammatory disease
- Decreased incidence of endometrial cancer
- Decreased incidence of ovarian cancer
- Decreased severity of acne

Oral Contraception

The contraceptive effect of the hormonal components contained in Loette 21 is based on the interaction of various factors, the most important of which are the inhibition of ovulation (by suppression of gonadotropin release) and changes in the cervical mucus (which increase the difficulty of sperm penetration into the uterus). Additionally, changes in the endometrium reduce the likelihood of implantation.

Acne

Acne treatment with Loette 21 is based on estrogen-induced increases in sex hormone binding globulin (SHBG). Because testosterone binds to SHBG, bioavailable testosterone is reduced. In addition, Loette 21 suppresses gonadotropin production, leading to decreased ovarian production of androgens, including androstenedione. Serum levels of 3 α-androstenediol glucuronide (a marker of peripheral 5 α-reductase activity) are also reduced. These biochemical changes produced by the co-administration of levonorgestrel and ethinyl estradiol are associated with improvement of acne in otherwise healthy women.

Clinical Studies

Oral Contraception

An open-label multicenter phase III clinical study was conducted in 1,447 women receiving Loette 21. 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. This rate includes patients who did not take the drug correctly. Cycle control was also evaluated by analyzing cycle characteristics such as duration and intensity of withdrawal bleeding and the incidence of breakthrough bleeding and amenorrhea. A total of 7,508 cycles were valid for cycle control analysis; the overall incidence of intermenstrual bleeding was low. Breakthrough bleeding alone and spotting alone occurred during 4.3% and 12.1% of cycles, respectively. Breakthrough bleeding and spotting occurred in 11.0% of the cycles, while breakthrough bleeding and/or spotting occurred in 27.3% of the cycles. Overall, 2.6% of cycles were amenorrheic. The length of withdrawal bleeding was 3 to 7 days in 86% of cycles, 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.

Acne

Two (2) randomised, double blind, placebo-controlled, 6-cycle, multicenter, phase III clinical studies were done to evaluate the efficacy and safety of levonorgestrel/ethinylestradiol (LNG/EE) 100 µg/20 µg for the treatment of moderate acne. Study 1 was conducted at 12 sites in the United States and at 1 site 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).

18. PHARMACOKINETICS

Levonorgestrel is rapidly and completely absorbed from the gastrointestinal tract. It is subject to minimal first-pass metabolism and is almost completely bioavailable following oral administration. Levonorgestrel is primarily metabolized by reduction of the A-ring followed by glucuronidation. The majority of an oral dose of levonorgestrel is eliminated as conjugates of glucuronide or sulfate with considerably smaller portions appearing as free metabolites. Approximately 43-45% of levonorgestrel is eliminated in the urine and approximately 32% in the feces.

After a single dose of Loette 21, maximum plasma concentrations ($C_{\max}$) of levonorgestrel of 2.8 ± 0.9 ng/ml (mean $\pm$ SD) are reached at 1.6 ± 0.9 hours. The area under the curve ($AUC_{0-\infty}$) is 35.2 ± 12.8 ng•hr/ml after a single dose. Following 21 days of Loette 21 therapy, steady state $C_{\max}$ values of 6.0 ± 2.7 ng/ml are attained at 1.5 ± 0.5 hours after the daily dose. The minimum plasma concentrations of levonorgestrel at steady state are 1.9 ± 1.0 ng/ml. The AUC_{0-24} at steady state is 68.3 ± 32.5 ng•hr/ml. The mean $AUC_{0-\infty}$ for levonorgestrel after a single dose is significantly lower than the mean AUC_{0-24} at steady state. In addition, sex hormone-binding globulin (SHBG) levels increased significantly from Day 1 (57 ± 18 nmol/l) to Day 21 (93 ± 40 nmol/l), induced by the daily administration of ethinylestradiol. Therefore, the non-linear kinetics of levonorgestrel are due to an increase in binding of levonorgestrel to SHBG. The elimination half-life for levonorgestrel in combination with ethinylestradiol is approximately 36 ± 13 hours at steady state.

Ethinylestradiol is rapidly and almost completely absorbed from the gastrointestinal tract. Ethinylestradiol undergoes extensive first-pass metabolism. The mean bioavailability is about 43% with marked interindividual variation. Ethinylestradiol is highly bound to albumin and induces an increase in the plasma concentration of SHBG. Ethinylestradiol is primarily metabolized by aromatic hydroxylation, but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronide or sulfate. Conjugated ethinylestradiol is excreted in bile and is subject to enterohepatic recirculation.

After a single dose of Loette 21, $C_{\max}$ values of ethinylestradiol of 62 ± 21 pg/ml are reached at 1.5 ± 0.5 hours. The $AUC_{0-\infty}$ is 653 ± 227 pg•hr/ml after a single dose. Following at least 6 daily doses of Loette 21 treatment, steady state $C_{\max}$ values of ethinylestradiol are 77 ± 30 pg/ml and are reached at 1.3 ± 0.7 hours. The AUC_{0-24} at steady state is 604 ± 231 pg•hr/ml. Following 21 days of treatment, steady state $C_{\max}$ values of ethinylestradiol of 82 ± 33 pg/ml are reached at 1.4 ± 0.6 hours after the daily dose. The minimum plasma concentrations of ethinylestradiol at steady state are 10.5 ± 5.1 pg/ml. The AUC_{0-24} at the end of 21 days of treatment is 776 ± 308 pg•hr/ml. The elimination half-life of ethinylestradiol in combination with levonorgestrel is 18 ± 4.7 hours at steady state.

19. PRECLINICAL SAFETY DATA

None

20. LIST OF EXCIPIENTS

Microcrystalline Cellulose, Lactose Monohydrate, Magnesium Stearate, Polacrillin Potassium, Opadry Pale Pink YS-1-14587A, Polyethylene Glycol 1450, Purified Water, Wax E Pharma.

21. INCOMPATIBILITIES

None known

22. STORAGE AND SHELF LIFE

Store below 30°C

KEEP OUT OF REACH OF CHILDREN

Observe “Expiry Date” (month/year) imprinted on outer carton.

23. NATURE AND CONTENTS OF THE CONTAINER

Loette 21 is supplied in blisters of 21 tablets.

24. MANUFACTURER

Manufactured by:

Pfizer Ireland Pharmaceuticals Unlimited Company
Little Connell, Newbridge,
W12 HX57,
Ireland

Under the authority of Pfizer Inc., New York, N.Y., USA.

*Trademark

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