- atorvastatin
- competitive inhibitors of sulfation in the gastrointestinal wall, such as ascorbic acid (vitamin C) and paracetamol
- cytochrome P450 3A4 isoenzyme inhibitors such as indinavir, fluconazole and troleandomycin*

Troleandomycin can increase the risk of intrahepatic cholestasis during concurrent use of combined oral contraceptives.

Ethinyloestradiol can affect the metabolism of other substances by inhibiting microsomal hepatic enzymes or by inducing hepatic conjugation of the drug, especially glucuronidation. Accordingly, plasma concentrations can either be increased (e.g. ciclosporin, theophylline, corticosteroids) or reduced (e.g. lamotrigine).

It has been reported that oral contraceptives may increase the risk of galactorrhea in patients treated with flunarizine.

The dosage of oral antidiabetics or insulin must be adjusted as needed.

The Summary of Product Characteristics of drugs used at the same time should be consulted in order to determine possible interactions.

** While ritonavir is an inhibitor of cytochrome P450 3A4, it has been shown that treatment with ritonavir reduces ethinyloestradiol serum levels. See above.*

Interactions with laboratory tests and other diagnostic procedures

Use of COC may cause certain physiological changes which may be reflected in the results of some laboratory tests such as:

- biochemical parameters of liver (e.g. decrease of bilirubin and alkaline phosphatase), thyroid (increase of T3 and T4 due to increase of TBG, decrease of free T3 absorption), adrenal (increase of cortisol plasma levels, increase of cortisol-binding globulin, decrease of dehydroepiandrosterone sulfate (DHEAS)) and renal function (increase of plasma creatinine levels and decrease of 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
- decrease of folic acid serum levels

Pharmacodynamic interactions

Concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir, dasabuvir with or without ribavirin, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir, may increase the risk of ALT elevations (see sections 4.3 and 4.4). Therefore, Loette-users must switch to an alternative method of contraception (e.g. progestagen-only contraception or non-hormonal methods) prior to starting therapy with these drug regimens. Loette can be restarted 2 weeks following completion of treatment with these drug regimens.

4.6 Use in special populations

Pregnancy

Before the first use of Loette pregnancy must be excluded.

If pregnancy occurs during treatment with a COC the COC must be immediately discontinued.

There is no definite evidence that the estrogen and progestin contained in a COC will harm the unborn child, if accidental pregnancy occurs during use of a COC.

Breast-feeding

Small amounts of contraceptive steroids and/or metabolites have been detected in breast milk of lactating mothers and some adverse effects for the nursed child such as jaundice and breast enlargement have been described. COC may affect lactation as they reduce the volume of breast milk and may change its composition

Use of a COC is usually not recommended as long as the child has not been completely weaned.

Pediatric use

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

Geriatric Use

COCs are not indicated for use in postmenopausal women.

4.7 Effects on ability to drive and use machines

Loette has no or only negligible effect on the ability to drive and use machines.

4.8 Undesirable effects

The definitions of frequency in the table have been based on the following categories:

Very common	≥ 1/10
Common	≥ 1/100, < 1/10
Uncommon	≥ 1/1.000, < 1/100
Rare	≥ 1/10.000, < 1/1.000
Very rare	<1/10.000
Not known:	cannot be estimated from the available data

The use of combined oral contraceptives has been associated with an increased risk of the following adverse effects:

- arterial and venous thrombotic and thromboembolic events (see section 4.4)
- cervical cancer and intraepithelial cervical neoplasms
- diagnosis of breast cancer
- an increased risk of benign liver tumors (e.g. focal-nodular hyperplasia, hepatic adenoma).

System organ class	Adverse effect
Infections and infestations	
Common:	vaginitis (incl. candidiasis)
Neoplasms benign, malignant and unspecified	
Very rare:	hepatocellular carcinoma
Immune system disorders	
Rare:	anaphylactic/anaphylactoid reactions with very rare cases of urticaria, angio-oedema* and severe reactions with respiratory symptoms and circulatory disturbances
Very rare:	exacerbation of lupus erythematosus
Metabolism and nutrition disorders	
Common:	changes in bodyweight (increase or decrease)
Uncommon:	changes of serum lipid levels including hypertriglyceridemia, changes in appetite (increase or decrease)
Rare:	decrease of serum folate levels**, glucose intolerance
Very rare:	exacerbation of porphyria
Psychiatric disorders	
Common:	mood swings, including depression, changes in libido
Nervous system disorders	
Very common:	headache, including migraine
Common:	nervousness, somnolence
Very rare:	exacerbation of chorea
Eye disorders	
Rare:	contact lens intolerance
Very rare:	optic neuritis***, retinal thrombosis
Cardiac disorders	
Uncommon:	blood pressure increase
Vascular disorders	
Very rare:	worsening of varicose veins
Gastrointestinal disorders	
Common:	nausea, vomiting, abdominal pain
Uncommon:	abdominal cramps, flatulence
Very rare:	pancreatitis, ischemic colitis
Not known:	inflammatory bowel disease (Crohn's disease, ulcerative colitis)
Hepatobiliary disorders	
Rare:	cholestatic jaundice
Very rare:	gallbladder diseases, including gall-stones****
Not known:	hepatocellular injury (hepatitis, hepatic function abnormal)
Skin and subcutaneous tissue disorders	
Common:	acne
Uncommon:	rash, chloasma (melasma) possibly permanent, hirsutism, alopecia
Rare:	erythema nodosum
Very rare:	erythema multiforme
Renal and urinary disorders	
Very rare:	haemolytic-uremic syndrome
Reproductive system and breast disorders	
Very common:	breakthrough bleeding, spotting
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:	accumulation of fluid / oedema

* Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

** Treatment with COC may result in a decrease of serum folate levels. This may be of clinical relevance, if the woman becomes pregnant shortly after discontinuation of the COC.

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

**** Oral contraceptives can exacerbate existing gall bladder diseases and accelerate the development of these diseases in previously asymptomatic women

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

Symptoms of overdosage of oral contraceptives in adults and children may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, somnolence/fatigue; withdrawal bleeding can occur in females. No specific antidote is available and treatment – where necessary – should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

COC work by suppressing gonadotrophins in a manner that inhibits ovulation, which leads to contraception.

Apart from the primary mechanism of ovulation inhibition they cause other changes such as changes of cervical mucus (making it more difficult for sperms to penetrate the uterus) and of the endometrium (reducing the likelihood of implantation).

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, hormonal contraceptives for systemic use, progestogens and estrogens, fixed combinations

ATC code: G03AA07

Upon regular and correct use the likely failure rate of a COC is about 0.1% per year, while the failure rate with the typical use of all types of oral contraceptives is about 5%. Efficacy of most contraceptive methods depends on the reliability of use. The likelihood of failure will increase if COC tablets are missed.

The etiology of acne is complex and there is evidence that an androgenic influence, in particular a stimulation of sebaceous glands, is a trigger for acne. Suppression of gonadotrophins by LOETTE leads to a reduced ovarian production of androgens, also of androstenedione. In addition, LOETTE significantly reduces the bioavailability of testosterone in serum by maintaining the oestrogen-induced increase in sex hormone binding globulin (SHBG). LOETTE also decreases serum levels of 3α-androstanediol glucuronide (a marker for peripheral 5α-reductase activity). These biochemical changes produced by the concomitant use of levonorgestrel and ethinyloestradiol coincide with the improvement of acne in otherwise healthy women.

5.3 Pharmacokinetic properties

Absorption:

Ethinyloestradiol:

- Is rapidly and completely absorbed from the gastrointestinal tract
- Absolute bioavailability is about 40-60%
- Single doses of Loette given to 22 fasting females:
  Peak serum concentrations: 62 ±21 pg/ml after 1.5 ± 0.5 hours
- Steady-state for Loette is reached earliest on day 6:
  Peak serum concentrations: 77 ± 30 pg/ml after 1.3 ± 0.7 hours
  Trough serum concentrations: 10.5 ± 5.1 pg/ml

Levonorgestrel:

- Is rapidly and completely absorbed from the gastrointestinal tract
- Absolute bioavailability: about 100%
- Single doses of Loette given to 22 fasting females:
  Peak serum concentrations: 2.8 ± 0.9 ng/ml after 1.6 ± 0.9 hours
- Steady-state for Loette is reached earliest on day 11:
  Peak serum concentrations: 6.0 ± 2.7 ng/ml after 1.5 ± 0.5 hours
  Trough serum concentrations: 1.9 ± 1.0 ng/ml

Table 1: Mean (SD) pharmacokinetic parameters of LOETTE over a dosing period of 21 days

	C_{max}	T_{max}	AUC	Cl/F	Vλz/F	SHBG
Levonorgestrel						
Day	ng/ml	h	ng•h/ml	ml/h/kg	l/kg	nmol/l
1	2.75 (0.88)	1.6 (0.9)	35.2 (12.8)	53.7(20.8)	2.66 (1.09)	57(18)
6	4.52 (1.79)	1.5 (0.7)	46.0 (18.8)	40.8 (14.5)	2.05 (0.86)	81(25)
21	6.00 (2.65)	1.5 (0.5)	68.3 (32.5)	28.4 (10.3)	1.43 (0.62)	93(40)
Unbound levonorgestrel						
Day	pg/ml	h	pg•h/ml	l/h/kg	l/kg	fu %
1	51.2 (12.9)	1.6 (0.9)	654 (201)	2.79 (0.97)	135.9 (41.8)	1.92 (0.30)
6	77.9 (22.0)	1.5 (0.7)	794 (240)	2.24 (0.59)	112.4 (40.5)	1.80 (0.24)
21	103.6 (36.9)	1.5 (0.5)	1177 (452)	1.57 (0.49)	78.6 (29.7)	1.78 (0.19)
Ethinyloestradiol						
Day	pg/ml	h	pg•h/ml	ml/h/kg	l/kg	
1	62.0 (20.5)	1.5 (0.5)	653 (227)	567 (204)	14.3 (3.7)	
6	76.7 (29.9)	1.3 (0.7)	604 (231)	610 (196)	15.5 (4.0)	
21	82.3 (33.2)	1.4 (0.6)	776 (308)	486 (179)	12.4 (4.1)	

Cl/F – Clearance of oral dose; Vλz/F – terminal volume of distribution; fu – fraction of unbound substance

Distribution

Ethinyloestradiol:

- Predominantly bound to serum albumin (about 98%)
- Induces increase of serum levels of sex hormone binding globulin (SHBG)

Levonorgestrel:

- Primarily bound to SHBG
- Increase of AUC measured from day 1 to 6 by 34% or from day 1 to 21 by 96%
- Increase of AUC of unbound levonorgestrel from day 1 to 6 by 25% or from day 1 to 21 by 83%
- The ethinyloestradiol-induced increase of SHBG results in an increased binding of levonorgestrel to SHBG leading to a non-linear kinetics for total levonorgestrel

Biotransformation

Ethinyloestradiol:

- Subject to first-pass metabolism (intestinal mucosa, liver) and enterohepatic circulation
- 2-hydroxylation by cytochrome P450 enzymes is the primary oxidative reaction
- A variety of hydroxylated and methylated metabolites are available as glucuronide and sulphate conjugates

Levonorgestrel:

- Is primarily metabolized by reduction at the Δ-4-3-oxo group and hydroxylation at the positions 2α, 1β and 16β and subsequent conjugation
- The majority of circulating metabolites are sulfates of 3α, 5β tetrahydrolevonorgestrel
- A part of unchanged levonorgestrel also circulates as 17β sulfates

Elimination

Ethinyloestradiol:

- Terminal elimination half-life of ethinyloestradiol in steady-state is approx. 18 + 4.7 hours
- Is excreted with the urine and feces as glucuronide and sulfate conjugates

Levonorgestrel:

- Terminal elimination half-life of levonorgestrel in steady-state is approx. 36 + 13 hours
- Levonorgestrel and its metabolites are predominantly excreted as glucuronides to a greater extent with the urine than with the feces

6. NONCLINICAL PROPERTIES

6.1 Animal toxicology or pharmacology

Toxicity studies have been carried out in animals with the two active components of LOETTE, levonorgestrel and ethinyloestradiol, and also with the combination.

The toxicological effects of levonorgestrel and ethinyloestradiol are therefore adequately known and constitute no risk for humans when used in therapeutic doses.

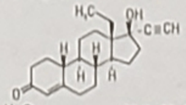
However, it should be remembered that sex steroids can certainly promote the growth of certain hormone-dependent tissues and tumours.

7. DESCRIPTION

Ethinyloestradiol is a white to creamy white, odorless crystalline powder. It is insoluble in water, soluble in alcohol, chloroform, ether, vegetable oils, and aqueous solutions of alkali hydroxides. Chemically, ethyiestradiol is 19-nor-17α-pregna-1, 3, 5 (10)-trieen-20-yne-3, 17-diol.

Chemical Structure

Levonorgestrel



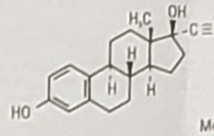
$C_{21}H_{28}O_2$ Mol. Wt. 312.5

Levonorgestrel is 13β-ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one.

Levonorgestrel is a white or nearly white, practically odorless, crystalline powder that is insoluble in water, sparingly soluble in alcohol, and soluble in chloroform and acetone. Chemically, levonorgestrel is (-)-ethyl-17-hydroxy-18, 19-dinor-17α-pregn-4-en-20-yn-3-one.

Chemical Structure:

Ethinyloestradiol



$C_{20}H_{24}O_2$ Mol. Wt. 296.4

Ethinylestradiol is 19-nor-17α-pregna-1,3,5(10)-trien-20yne-3,17β-diol.

Loette is available in the form of uncoated tablet.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

None

8.2 Shelf-life

Refer the outer carton for the date of expiry. The date of expiry is the last day of the month.

8.3 Packaging information

21 tablets are blister packed using rear printed Aluminium foil and front clear PVC foil.

All strengths/presentations mentioned in this document might not be available in the market.

8.4 Storage and handling instructions

Store below 30°C.

Protect from moisture.

Keep out of the reach of children.

9. PATIENT COUNSELLING INFORMATION

- Counsel the woman about correct usage of the tablets.
- Counsel the woman that irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use.
- Counsel the woman on the warnings and precautions associated with use of Loette.
- Women should be advised that hormonal contraceptives do not protect against HIV infections (AIDS)and other sexually transmitted diseases.
- Consel the woman that Use of COC may increase the risk of venous and arterial thrombotic and thromboembolic events such as myocardial infarction, stroke, deep vein thrombosis or pulmonary embolism.
- Counsel the woman to seek urgent medical attention if any of the below symptoms arise:
  - unilateral leg pain and/or swelling,
  - sudden onset of marked chest pain which may or may not radiate to the left arm,
  - sudden onset of dyspnea,
  - sudden onset of cough,
  - unusual, severe and persistent headache,
  - sudden partial or complete loss of vision, diplopia, slurred speech or aphasia, vertigo,
  - collapse with or without focal seizure,
  - weakness or numbness in one half of the body or in a limb with sudden onset,
  - motor disturbance,
  - acute abdominal pain.

10. DETAILS OF MANUFACTURER

1. Pfizer Limited, 45, Mangalam Main Road, Mangalam village, Villianur Commune, Puducherry – 605110, India

Or

2. Pfizer Limited, Plot No. L-137, Phase III A, Verna Industrial Estate, Verna, Goa-403722, India

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Initial permission issued under rule 122 – B/C dated 17.06.1999 & Import & Marketing Permission No. MF-831/2010 dated 13.10.2010

12. DATE OF REVISION

This package insert was last revised in January 2022

Please refer to the current Package Insert for updated information LPDLTE012022

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Licensed User – Pfizer Limited, India

LPDLTE012022

134_0622

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

LEVONORGESTREL AND ETHINYLOESTRADIOL TABLETS I.P.

LOETTE®

Pfizer

PATIENTS SHOULD BE COUNSELED THAT THIS PRODUCT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.

1. GENERIC NAME

Levonorgestrel and Ethinyloestradiol Tablets I.P.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:

Levonorgestrel I.P.	0.10 mg
Ethinyloestradiol I.P.	0.02 mg

List of Excipients

Lactose (70 mesh), Microcrystalline Cellulose (PH101), Indion 234, Magnesium Stearate I.P.

All strengths/ presentations may not be available in the market.

3. DOSAGE FORM AND STRENGTH

Dosage Form: Uncoated Tablet

Strength: Levonorgestrel I.P. 100 mcg and Ethinyloestradiol I.P. 20 mcg tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

- Loette is indicated for the prevention of pregnancy in women who elect to use an oral contraceptive.
- For the treatment of moderate acne vulgaris in women ≥18 years of age who have no known contraindications to oral contraceptive therapy, desire contraception, and have achieved menarche.

4.2 Posology and method of administration

To be swallowed whole, with some liquid.

The tablets 1-21 contain active substance (active tablets).

Tablets must be taken in the order directed on the package every day at about the same time. The active tablets are to be taken daily for 21 consecutive days. Withdrawal bleed usually starts on days 2-3 after the last active tablet, and may not have finished before the next pack is started.

Starting with the use of Loette:

No preceding hormonal contraceptive use in the past month:

The first tablet is to be taken on the first day of the menstrual period (i.e. the first day after menstrual bleeding has started).

Intake of Loette may also be started on days 2 to 5 of the menstrual cycle (e.g. start on a Sunday), but in this case, additional use of a non-hormonal method of contraception (e.g. condom, spermicide) is recommended for the first 7 days of the monthly cycle for reasons of safety.

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

Use of Loette should preferably be started on the day after intake of the last active tablet of the previous COC but at the latest on the day of the normal tablet-free interval or after taking the last drug-free tablet of the previous COC.

With previous use of a ring or a patch, use of the tablets should be started immediately after removal of the ring/patch still on the same day.

Changing from a progestin-only method to contraception (progestin-only pill, implant, intrauterine device [IUD], injection):

- The use of a progestin-only pill may be terminated on any day, with the use of Loette starting on the following day
- Use of Loette should be started on the day of removal of a progestin-only implant or a progestin-only IUD.
- Use of Loette should be started on the day of the scheduled next injection of a progestin-only product.

In all these cases the user must be advised that for reasons of safety a non-hormonal method of contraception should be used for the first 7 days of use of Loette.

Following first-trimester abortion:

Loette may be started immediately. Additional contraceptive measures are not needed.

Post-partum use:

Since the immediate post-partum period is associated with an increased risk of thromboembolism, Loette should be started no earlier than day 28 days post-partum. The user should be advised to use a non-hormonal back-up method (e.g. condom, spermicide) for the first 7 days of taking Loette for reasons of safety. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman must wait for her first menstrual period. See sections 4.4 and 4.6 for use in lactating women.

Management of missed tablets:

Contraceptive protection may be reduced if active tablets are missed, and particularly if the missed tablets extend the tablet free interval.

- If one active tablet is missed, but **is taken within the next 12 hours** no additional contraceptive measures are needed. Subsequent tablets should be taken at the usual time.
- If one active tablet is missed and **is taken more than 12 hours late** or if more than one active tablet is missed, contraceptive protection may be reduced. The last tablet missed should be taken as soon as it is remembered, even if this means taking two tablets in one day. Subsequent tablets should be taken at the usual time. In addition, a non-hormonal back-up method of birth control (e.g. condom, spermicide) should be used for the next seven days for reasons of safety.
- If the seven days during which back-up is required extend beyond the last active tablet in the current pack, the next pack must be started as soon as the current pack is finished, no gap should be left between packs. This will prevent an extended break in taking active tablets and thus reduce the risk of ovulation. 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 the days of taking active tablets. 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.

Advice in case of vomiting:

If vomiting occurs within 4 hours after tablet-taking, absorption may not be complete. As explained below, the tablets from a back-up pack must be taken. In such an event, the advice concerning "Management of missed tablets" is applicable (see above).

The woman must take the appropriate active tablet(s) needed from a back-up pack.

Delaying a period

To delay a period, the next pack of Loette should be started immediately skipping the tablet free interval. The extension can be carried on for as long as wished until the end of the second pack. During the extension the woman may experience breakthrough-bleeding or spotting. Regular intake of Loette is then resumed after the usual 7-day tablet-free interval.

4.3 Contraindications

Combined oral contraceptives (COC) such as LOETTE are contraindicated with any of the following conditions. If any of the conditions listed below occurs for the first time during the use of a COC, use of the COC must be immediately terminated:

- Hypersensitivity to the active substances or any of the excipients listed in section 2
- Cerebrovascular disease or coronary heart disease
- Current or previous arterial or venous thromboembolic events (such as deep vein thrombosis, pulmonary embolism, myocardial infarction) or cerebrovascular events
- Current or previous prodromes of thrombosis (e.g. transitory ischemic attacks, angina pectoris)
- Hereditary or acquired predisposition for venous or arterial thrombosis (e.g. APC resistance, antithrombin III deficiency, protein C and protein S deficiency, hyperhomocysteinemia and antiphospholipid antibodies (anticardiolipid antibodies, lupus anticoagulant)
- Valvular heart disease
- Cardiac arrhythmias
- Migraine with focal neurological symptoms, such as aura
- Diabetes mellitus with vascular changes
- Uncontrolled hypertension
- Severe lipid metabolism disorder
- Known or suspected breast cancer or other known or suspected estrogen-dependent neoplasms
- Hepatic adenomas or carcinomas or active liver disease, as long as liver function has not returned to normal
- Undiagnosed vaginal bleeding
- Pancreatitis associated with severe hypertriglyceridemia (current or previous)
- Loette is contraindicated for concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir, dasabuvir, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Smoking increases the risk of severe cardiovascular side effects from the use of combined oral contraceptives (COC). This risk increases with age and the extent of smoking. It is especially high in women over 35 years of age. Women aged over 35 years who smoke should consider other methods of contraception.

In the presence of any of the risk factors/conditions listed below the benefit of oral contraceptives must be weighed against the potential risks on an individual basis and discussed with the user before starting contraception with a combined oral contraceptive. If any of these conditions or risk factors worsens or develops for the first time, the user is advised to consult her doctor. The treating physician must then decide whether to stop the use of oral contraceptives.

Venous and arterial thrombosis and thromboembolism

Use of COC increases the risk of venous and arterial thrombotic and thromboembolic events such as myocardial infarction, stroke, deep vein thrombosis or pulmonary embolism.

There have also been isolated reports of thrombosis in other blood vessels, such as hepatic, mesenterial, cerebral or retinal veins or arteries. It has not yet been fully elucidated whether their occurrence is associated with the use of combined oral contraceptives.

The potential symptoms of venous or arterial thrombotic/thromboembolic events or cerebrovascular events include: unilateral leg pain and/or swelling, sudden onset of marked chest pain with or without irradiation to the left arm, sudden onset of dyspnea, sudden onset of cough, unusual, severe and persistent headache, sudden partial or complete loss of vision, diplopia, slurred speech or aphasia, vertigo, collapse with or without focal seizure, weakness or numbness in one half of the body or in a limb with sudden onset, motor disturbance, acute abdomen. Upon the first signs or symptoms suggestive of an imminent complication the use of Loette should be stopped and the causes should be clarified.

Venous thrombosis and thromboembolism

The use of any combined oral contraceptives (COC) carries an increased risk of venous thromboembolic events (VTE) compared with no use. The excess VTE risk is highest during the first year a woman ever uses a COC. This increased risk is less than the risk of VTE in a pregnancy, which is estimated as 60 cases per 100,000 pregnancies. VTE is fatal in 1-2% of cases.

The absolute VTE risk (incidence) with levonorgestrel-containing COC with 30 mg ethinyloestradiol is about 20 cases per 100.000 women-years of use.

The risk of venous thrombotic and thromboembolic events is further increased in women with a disorder predisposing for venous thrombosis and thromboembolism.

Examples for disorders predisposing for venous thrombosis and thromboembolism include:

- obesity (BMI ≥ 30 kg/m²)
- surgery, trauma with increased risk of thrombosis
- recent delivery or second-trimester abortion
- prolonged immobilization
- increasing age
- familial predisposition. If a marked predisposition is suspected, the woman should be referred to a specialist for advice and decision on the use of a COC.
- there is no consensus on the potential role of varicose veins and superficial thrombophlebitis in venous thromboembolism.

In the case of planned surgery, the use of Loette should be discontinued if possible one month prior to the operation and not resumed until full remobilisation. Use should also be stopped in the case of prolonged immobilisation.

As the thromboembolic risk is increased during the time immediately after delivery, the use of Loette in non-nursing females and females post second-trimester abortion should not be started any earlier than 28 days post-partum (see section 4.2).

Arterial thrombosis and thromboembolism

Use of Loette increases the risk of arterial thrombosis and thromboembolism. There have been reports of myocardial infarction and cerebrovascular events (ischemic and hemorrhagic stroke, transitory ischemic attacks). For information on retinal vascular thromboses see "Eye Disorders".

The risk of arterial thrombosis and thromboembolism in association with the use of oral contraceptives increases in the presence of various risk factors and must be carefully assessed in affected women.

Risk factors for arterial thrombotic and thromboembolic events include:

- smoking
- hypertension
- hyperlipidemia
- obesity (BMI >30 kg/m²)
- advanced age
- familial predisposition. If a marked predisposition is suspected, the woman should be referred to a specialist for advice and decision on the use of a COC.
- migraine
- atrial fibrillation
- valvular heart disease

Upon first occurrence or worsening of migraine or occurrence of severe, recurrent or persisting headache the COC must be discontinued and the causes evaluated.

Women with migraine (especially migraine with aura) may have an increased risk of stroke. See section 4.3.

Presence of a major risk factor or of multiple risk factors for venous or arterial thromboembolic disorders may be considered as a contraindication.

Ocular lesions

There have been reports of thrombosis of retinal vessels during the use of oral contraceptives potentially resulting in partial or complete loss of vision. At the first signs or symptoms of changes in vision, occurrence of bulbar protrusion or diplopia, papillary edema or lesions of the retinal vessels, the use of COC should be discontinued until the causes have been clarified.

Blood pressure

An increase in blood pressure during the use of oral contraceptives has been reported.

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

Use of COC in women with uncontrolled hypertension is contraindicated. See section 4.3.

Cancer of reproductive organs

Cervical cancer

The major risk factor for cervical cancer is a persistent infection with human papillomavirus.

Some studies have suggested that the use of COC in some female populations may be associated with an increased risk of cervical intraepithelial neoplasms or invasive cervical carcinoma.

However, it has not yet been clarified to what extent this result is also influenced by differences in sexual behavior and other factors. In the presence of unclarified abnormal genital bleeding appropriate diagnostic evaluation is indicated.

Breast cancer

A meta-analysis from 54 epidemiological studies reported a slightly increased risk of having breast cancer diagnosed in COC users as compared to non-users. This increased risk gradually decreases within 10 years after discontinuation of the COC. These studies provide no proof of a causal relationship. The increased risk for higher number of breast cancers may arise through the increased probability of earlier detection in users of oral contraceptives (due to the more regular checks), the effects of COC use, or a combination of both. Since breast cancer is rare in women under 40 years of age, the number of additionally diagnosed breast cancers in women who are taking a combined oral contraceptive, or who have taken one until recently, is small in proportion to the overall risk of breast cancer. The diagnosed breast cancers in COC users of combined oral contraceptives tend to be clinically less advanced than in non-users.

Hepatic neoplasms/liver diseases

In very rare cases hepatic adenoma and in isolated cases hepatocellular carcinoma have been reported during the use of combined oral contraceptives. The risk appears to increase with the duration of use of COC. Rupture of a liver adenoma may result in death from intra-abdominal hemorrhage. If severe epigastric pain, hepatomegaly or signs of intraabdominal bleeding develops during the use of combined oral contraceptives, differential diagnosis of a hepatic tumor should be considered.

Women with COC-associated cholestasis or cholestasis during pregnancy have an increased risk of developing a liver tumour during use of COC. If such patients receive combined oral contraceptives, they should be regularly monitored. If cholestasis recurs, the COC should be stopped.

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 contraception and consult their doctor.

Acute or chronic hepatic dysfunction may necessitate immediate discontinuation of the COC until liver function has normalized.

Precautions

Medical examination

Prior to the initiation or reinstitution of treatment with combined oral contraceptives a complete personal and family medical history must be taken and pregnancy must be excluded. A medical examination being focused on contraindications (section 4.3) and warnings (section 4.4) should be taken and should be repeated at least once yearly during the use of the oral contraceptive. Periodical clinical controls will be important as contraindications or risk factors may emerge for the first time during use of combined oral contraceptives. Frequency and scope of these examinations should be in accordance with the applicable guidelines and individualized for each women. However, at least the following examinations should be performed: blood pressure, examination of breast, abdomen and pelvic organs including cervix cytology.

Users must be informed that the medicinal product will not protect against HIV infection (AIDS) or other sexually transmitted diseases.

Effect on carbohydrate and lipid metabolism

Effects on peripheral insulin resistance and glucose intolerance have been reported for users of COC. COC users with limited glucose tolerance or diabetes mellitus will require careful monitoring. See section 4.3.

Undesirable changes in lipid levels will occur in a small number of users of oral contraceptives. A non-hormonal method of contraception should be considered for women with uncontrolled dyslipidaemia. Persistent hypertriglyceridemia may occur in a small percentage of COC users. An increase in plasma triglycerides can result in pancreatitis and other complications.

Estrogens will increase high-density-lipoprotein (HDL)-cholesterol serum levels while decrease of HDL-cholesterol has been reported for many progestogens. Some progestogens may lead to an increase of low-density-lipoprotein (LDL) levels and make treatment of hyperlipidemia more complicated. The overall effect of a COC will depend on the balance between estrogen and progestogen dose and on the type and absolute amount of progestin in the contraceptive. The content of both hormones should be considered when choosing a COC.

Women who decide to use a COC and are under concurrent treatment for hyperlipidaemia must be closely monitored during the use of the COC.

Genital bleeding

Some women may have no withdrawal bleeding during tablet free interval. If the COC has not been taken as per the instructions before the first amenorrheic cycle, or if two consecutive withdrawal bleeds are missed, tablet-taking should be stopped and a non-hormonal contraceptive method used until pregnancy has been ruled out.

Breakthrough bleeding or spotting can occur during use of a COC, especially during the first three months of use. If such bleeding persists, or occurs for the first time after long-term use, a non-hormonal cause should be considered and evaluated by adequate diagnostic assessment. If pathological causes have been excluded and the bleeding persists, the continued use of Loette or a change to another product should be considered.

In a few cases, amenorrhea (possibly with anovulation) or oligomenorrhea can occur after the pill is stopped. This is particularly likely if this already occurred before treatment started.

Depression

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating treatment.

Other

Diarrhea and/or vomiting may reduce hormone absorption resulting in decreased serum concentrations. See sections 4.2 and 4.5.

Strict medical supervision must be ensured for the first appearance of underlying diseases during a pregnancy or use of combined oral contraceptives, or a deterioration that may occur in these conditions and/or in patients with the following existing diseases or a history thereof: metabolic disorders (diabetes, hyperlipidemia), hypertension, family history of vascular diseases, previous superficial thrombophlebitis, varicose veins, jaundice and/or pruritus associated with cholestasis, gallstones, porphyria, herpes gestationis, otosclerosis, asthma, epilepsy, migraine, chorea, cardiac, renal or hepatic dysfunction, systemic lupus erythematosus, obesity, multiple sclerosis, tetany, depression, hemolytic-uremic syndrome and sickle-cell anemia.

Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

Crohn's disease and ulcerative colitis have been associated with the use of COC.

Chloasma may occasionally be seen, especially in women with a history of chloasma gravidarum. Women predisposed for chloasma should avoid exposure to sunlight or UV irradiation during use of a COC to minimise the risk of an exacerbation.

Elderly patients

COC are not indicated for use in postmenopausal women.

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 or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinyloestradiol-containing medications such as combined hormonal contraceptives (CHCs). ALT elevations have also been observed with HCV anti-viral medicinal products containing glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir (see sections 4.3 and 4.5).

Loette contains lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Drugs interactions

Interactions between ethinyloestradiol and other drugs can lead to increased or decreased serum concentrations of ethinyloestradiol.

Reduced serum concentrations of ethinyloestradiol can result in the increased occurrence of breakthrough bleeding and menstrual irregularities and may even reduce effectiveness of the oral contraceptive.

During concomitant use of substances that may lead to decreased EE serum concentrations, it is recommended that an additional non-hormonal back-up method of birth control (such as condoms) be used for the time of the use of these substances and for 7 days thereafter in addition to the regular use of Loette.

With substances (e.g. rifampicin, see below) inducing microsomal hepatic enzymes with a resultant decrease of EE serum levels it is advisable to continue the additional use of non-hormonal methods for prolonged time (For the time of treatment and for another 28 additional days. If treatment with the co-medication extends beyond the time of the active tablets from the blister of the COC, the next blister of the COC should be started directly without the usual tablet-free interval.). Depending on dose, duration of use and rate of elimination of the inducing substance it may sometimes take several weeks until enzyme induction has completely subsided.

Upon prolonged use of such substances COC should not be used as primary contraceptive.

Substances that may decrease serum EE concentrations include:

- any substances that reduce gastrointestinal transit time and thus reduce EE absorption
- substances that induce microsomal hepatic enzymes, e.g. rifampicin, rifabutin, barbiturates, primidone, phenylbutazone, phenytoin, dexamethasone, griseofulvin, topiramate, various protease inhibitors, modafinil, carbamazepine (presumably also oxacarbazepine and felbamat)
- St. John's wort (*Hypericum perforatum*) and ritonavir* (possibly through the induction of hepatic microsomal enzymes)

Substances that may increase serum EE concentrations include: