

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

# Levonorgestrel and Ethinyloestradiol Tablets I.P.

## OVRAL<sup>®</sup> L Tablets



**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 strip contains 21 uncoated tablets, each tablet containing:

Levonorgestrel I.P.	0.15 mg
Ethinyloestradiol I.P.	0.03 mg

#### List of Excipients

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

### 3. DOSAGE FORM AND STRENGTH

Dosage Form: Uncoated Tablet

Strength: Levonorgestrel I.P. 150 mcg and Ethinyloestradiol I.P. 30 mcg

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic Indication

Ovral L is indicated for the prevention of pregnancy in women who elect to use an oral contraceptive.

<sup>®</sup> Trademark Proprietor – Wyeth LLC, USA  
Licensed User – Pfizer Limited, India

## 4.2 Posology and Method of Administration

### How to take Ovral L

Ovral L is available in pack containing 21 active tablets.:

Tablets must be taken in the order directed on the package every day at about the same time. One active tablet is to be taken daily for 21 consecutive days then 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.

### How to start Ovral L

- No hormonal contraceptive use within the preceding month

The user should begin taking Levonorgestrel and Ethinyloestradiol by 5<sup>th</sup> day of menstrual cycle counting first day of bleeding as Day1.

- Switching from another COC

Preferably, Levonorgestrel and Ethinyloestradiol 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 interval or inactive tablet 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 Levonorgestrel and Ethinyloestradiol should begin the following day.
- Levonorgestrel and Ethinyloestradiol use should begin on the same day that a progestin-only implant or a progestin-only IUD is removed.
- Levonorgestrel and Ethinyloestradiol 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 Levonorgestrel and Ethinyloestradiol use.

- Following first-trimester abortion

Levonorgestrel and Ethinyloestradiol use may begin immediately. Additional contraceptive measures are not needed.

- Postpartum

Because the immediate postpartum period is associated with an increased risk of thromboembolism, Levonorgestrel and Ethinylloestradiol use should begin no sooner than the 28<sup>th</sup> 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 Levonorgestrel and Ethinylloestradiol use. However, if intercourse has already occurred, pregnancy must be ruled out before Levonorgestrel and Ethinylloestradiol use is begun; otherwise, the woman must wait until her first menstrual period before beginning Levonorgestrel and Ethinylloestradiol use. See sections 4.4 Special Warnings and Precautions for Use and 4.6 Use in Special Population.

### **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.

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.

The following instructions are an alternative for the management of missed tablets:

- 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.

### **Advice in case of vomiting and/ or diarrhea**

If vomiting or diarrhea occurs within 4 hours after tablet taking, 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 4.2 Posology and Method of Administration).

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

### **4.3 Contraindications**

Levonorgestrel and Ethinyloestradiol must not be used in women with any of the following conditions:

- Deep vein thrombosis (current or history)
- Thromboembolism (current or history)
- Cerebrovascular or coronary artery disease
- Thrombogenic valvulopathies
- Thrombogenic rhythm disorders
- Hereditary or acquired thrombophilias
- Headache with focal neurological symptoms, such as aura
- Diabetes with vascular involvement
- Uncontrolled hypertension
- Known or suspected carcinoma of the breast or other known or suspected estrogens dependent neoplasia
- 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 history)
- Known or suspected pregnancy
- Hypersensitivity to any of the components of Levonorgestrel and Ethinyloestradiol tablets.

COCs are contraindicated for concomitant use with certain anti-viral hepatitis C virus (HCV) medicinal products such as ombitasvir, paritaprevir, ritonavir and dasabuvir (See sections 4.4 Special Warnings and Precautions for Use and 4.5 Drugs Interactions).

#### 4.4 Special Warnings and Precautions for Use

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.

##### 1. VENOUS AND ARTERIAL THROMBOSIS AND THROMBOEMBOLISM

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

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

###### *a. 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 4.4 Special Warnings and Precautions for Use - 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 1-2% of cases.

Epidemiological studies have shown that the incidence of venous thromboembolism in users of low-estrogen oral contraceptives (<50 mcg Ethinylloestradiol) 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.

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 (See section 4.3 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.

Since the immediate post-partum period is associated with an increased risk of thromboembolism, COCs should be started no earlier than the 28<sup>th</sup> postpartum day following either delivery in a nonlactating woman or or second-trimester abortion.

*b. 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 ischaemic attack). For information on retinal vascular thrombosis, (See section 4.4 Special Warnings and Precautions for Use - 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 are:

- smoking
- hypertension
- hyperlipidemias
- obesity
- increasing age

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

Further risk factors, which represent contraindications for the use of COCs, are listed in (See section 4.3 Contraindications).

## 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.

## 3. BLOOD PRESSURE

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

In women with hypertension, a history of hypertension or hypertension related diseases (including certain renal diseases), another method of contraception may be preferable. If COCs are used in such cases, close monitoring is recommended and, 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 4.3 Contraindications).

## 4. CARCINOMA OF THE REPRODUCTIVE ORGANS

### a. 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.

b. 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 (RR = 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. 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 COC they 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 nonhormonal 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.

Hepatitis C

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



## 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 4.3 Contraindications).

## 7. IMMUNE

### *Angioedema*

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

## **PRECAUTIONS**

### 1. MEDICAL EXAMINATION

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.

### 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 4.3 Contraindications).

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

### 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 contraception 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 an ovulation) or oligomenorrhea, especially when such a condition was preexistent.

### 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 alternate method of contraception in an attempt to determine whether the symptom is drug-related.

### 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 sections 4.2 Posology and Method of Administration and 4.5 Drugs Interactions).

## 4.5 Drugs Interactions

Interactions between Ethinylloestradiol (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 sections 4.3 Contraindications and 4.4 Special Warnings and Precautions for Use).

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 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 Levonorgestrel and Ethinylloestradiol. 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 P 450 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 P 450 3A4, treatment with ritonavir has been shown to decrease EE serum concentrations (see above).

## **INTERFERENCE WITH LABORATORY AND OTHER DIAGNOSTIC TESTS**

### **Effects on laboratory parameters**

The use of COCs may cause certain physiologic changes which may be reflected in the results of certain laboratory tests, including

- a. Biochemical parameters of liver function (including a decrease in bilirubin and alkaline phosphatase), thyroid function (increased total T<sub>3</sub> and T<sub>4</sub> due to increased TBG, decreased free T<sub>3</sub> resin uptake), adrenal function (increased plasma cortisol, increased cortisol binding globulin, decreased dehydroepiandrosterone sulfate (DHEAS), and renal function (increased plasma creatinine and creatinine clearance).
- b. Plasma levels of (carrier) proteins, such as corticosteroid-binding globulin and lipid/lipoprotein fractions
- c. Parameters of carbohydrate metabolism
- d. Parameters of coagulation and fibrinolysis
- e. Decreased serum folate levels

## 4.6 Use in Special Populations

### 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 Section 4.3 Contraindications).

### 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.

### 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

There is no clinical data available on effect of levonorgestrel and Ethinylloestradiol on ability to drive or use machines.

## 4.8 Undesirable Effects

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

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

(See section 4.4 Special Warnings and Precautions for Use).

<b>System Organ Class</b>	<b>Adverse Reaction</b>
<b><i>Infections and Infestations</i></b>	
Common	Vaginitis, including candidiasis
<b><i>Neoplasms benign, malignant, and unspecified</i></b>	
Very Rare	Hepatocellular carcinomas
<b><i>Immune system disorders</i></b>	
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
<b><i>Metabolism and nutrition disorders</i></b>	
Uncommon	Changes in appetite (increase or decrease)
Rare	Glucose intolerance
Very Rare	Exacerbation of porphyria
<b><i>Psychiatric disorders</i></b>	
Common	Mood changes, including depression; changes in libido
<b><i>Nervous system disorders</i></b>	
Very common	Headache, including migraines
Common	Nervousness; dizziness
Very Rare	Exacerbation of chorea
<b><i>Eye disorders</i></b>	
Rare	Intolerance to contact lenses
Very Rare	Optic neuritis;* retinal vascular thrombosis
<b><i>Vascular disorders</i></b>	
Very Rare	Aggravation of varicose veins
<b><i>Gastrointestinal disorders</i></b>	
Common	Nausea; vomiting; abdominal pain
Uncommon	Abdominal Cramps; bloating
Very Rare	Pancreatitis, ischemic colitis
Unknown	Inflammatory bowel disease (Crohn's Disease, ulcerative colitis)
<b><i>Hepato-biliary disorder</i></b>	
Rare	Cholestatic jaundice

Very Rare	Gallbladder disease, including gallstones**
Unknown	Hepatocellular injury (e.g. hepatitis, hepatic function abnormal)
<b><i>Skin and subcutaneous tissue disorders</i></b>	
Common	Acne
Uncommon	Rash; chloasma (melasma), which may persist; hirsutism; alopecia
Rare	Erythema nodosum
Very Rare	Erythema multiforme
<b><i>Renal and urinary disorders</i></b>	
Very Rare	Hemolytic uremic syndrome
<b><i>Reproductive system and breast disorders</i></b>	
Very Common	Breakthrough bleeding/spotting
Common	Breast pain, tenderness, enlargement, secretion; dysmenorrhea; change in menstrual flow; change in cervical ectropion and secretion; amenorrhea
<b><i>General disorders and administration site conditions</i></b>	
Common	Fluid retention/edema
<b><i>Investigations</i></b>	
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.

## 4.9 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.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Mechanism of Action

COC suppresses gonadotrophins in a manner that inhibits ovulation, which leads to contraception.

## 5.2 Pharmacodynamic Properties

When taken consistently and correctly, the probable failure rate of COC 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.

## 5.3 Pharmacokinetic Properties

### Absorption:

Ethinylestradiol and levonorgestrel are rapidly and almost completely absorbed from the gastrointestinal tract. Ethinylestradiol is subject to considerable first-pass metabolism with a mean bioavailability of 40-45%. Levonorgestrel does not undergo first-pass metabolism and is thereby completely bioavailable.

### Metabolism:

Levonorgestrel is extensively plasma protein bound both to sex hormone binding globulin (SHBG) and albumin. Ethinylestradiol, however, is bound in plasma only to albumin and enhances the binding capacity of SHBG. Following oral administration, peak plasma levels of each drug occur within 1 to 4 hours.

### Excretion:

The elimination half-life for Ethinylestradiol is approximately 25 hours. It is primarily metabolized by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present both free and as conjugates with glucuronide and sulfate. Conjugated Ethinylestradiol is excreted in bile and subject to enterohepatic recirculation. About 40% of the drug is excreted in the urine and 60% is eliminated in the feces.

The elimination half-life for levonorgestrel is approximately 24 hours. The drug is primarily metabolized by reduction or hydroxylation followed by conjugation with sulfate and glucuronide. About 60% of levonorgestrel is excreted in the urine and 40% is eliminated in the feces.

## 6. NONCLINICAL PROPERTIES

### 6.1 Animal Toxicology or Pharmacology

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## 7. DESCRIPTION

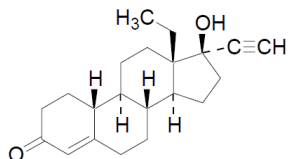
Ethinylestradiol is a white to creamy white, odorless crystalline powder. It is insoluble in water, soluble in alcohol, chloroform, ether, vegetable oils, and aqueous solutions of



alkali hydroxides. Chemically, Ethyloestradiol is 19-nor-17 $\alpha$ -pregna-1, 3, 5 (10)-trien-20-yne-3, 17-diol.

Chemical Structure:

### Levonorgestrel



C<sub>21</sub>H<sub>28</sub>O<sub>2</sub>

Mol. Wt. 312.5

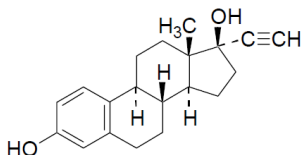
Levonorgestrel is 13 $\beta$ -ethyl-17 $\beta$ -hydroxy-18,19-dinor-17 $\alpha$ -pregn-4-en-20-yn-3-one.

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-17 $\alpha$ -pregn-4-en-20-yn-3-one.

Chemical Structure:

### Ethinylestradiol

Ethinylestradiol



C<sub>20</sub>H<sub>24</sub>O<sub>2</sub>

Mol. Wt. 296.4

Ethinylestradiol is 19-nor-17 $\alpha$ -pregna-1,3,5(10)-trien-20yne-3,17 $\beta$ -diol.

Ovral L is available in the form of uncoated tablet.

## **8. PHARMACEUTICAL PARTICULARS**

### **8.1 Incompatibilities**

None

### **8.2 Shelf-life**

30 months

### **8.3 Packaging Information**

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

### **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.
- Counsel 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, Plot No. L-137, Phase III-A, Verna Industrial Estate, Verna, Goa-403722, India

Or

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

**11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE**

Manufacturing License\* No. 545 dated 1st Dec 2019 & 13233686 dated 12th Oct 2018  
(\* The manufacturing license is renewed every 5 years as per Indian regulations)

**12. DATE OF REVISION**

February 2022