Norgestrel & Ethinyloestradiol Tablets I.P.

OVRAL® G Tablets

1. TRADE NAME OF THE MEDICINAL PRODUCT

OVRAL G

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:

Norgestrel I.P.	0.5 mg
Ethinyloestradiol I.P.	0.05 mg

For full list of excipients please see section 6.1.

3. PHARMACEUTICAL FORM

Ethinyloestradiol is a white to creamy white, odourless, crystalline powder. It is insoluble in water; soluble in alcohol, chloroform, ether, vegetable oils, and in solutions of fixed alkali hydroxides. Chemically, ethinyl estradiol is 19-Nor-17α-pregna-1, 3, 5 (10)-trien-20-yne-3, 17-diol.

Norgestrel is a white or practically white, practically odourless, crystalline powder that is insoluble in water, sparingly soluble in alcohol, and freely soluble in chloroform. Chemically, Norgestrel is (±)-13-Ethyl-17-hydroxy-18, 19-dinor-17 α -pregn-4-en-20-yn-3-one.

Ovral G is available in tablet form.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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Licensed User – Pfizer Limited, India

OVRAL G is indicated for treatment of postponement of menses, endometriosis; dysfunctional uterine bleeding, including emergency treatment of acute episodes, dysmenorrhea, and menstrual irregularities.

4.2 Posology and Method of Administration

Tablets for oral use

How to take Ovral G

Postponement of Menses
For this purpose, one tablet should be taken daily starting with the 20th day i.e. eight days prior to expected date of menstruation. With this dosage, the menstrual period can be postponed to the 40th day i.e. about two weeks beyond the expected date.

Endometriosis
Treatment should be continuous (noncyclic) with one Ovral G tablet daily for periods of 6 to 12 months. If spotting or breakthrough bleeding occurs, dosage may be increased to 2 or, rarely 3, tablets daily.

Dysfunctional Uterine Bleeding
For the emergency treatment of acute bleeding, the initial dose is 2 to 4 tablets daily until bleeding stops. Subsequently, the daily dose is reduced to 1 to 2 tablets and continued until a total of 20-21 days of treatment have been taken. The patient should be advised that withdrawal bleeding will occur within 3 days of cessation.

In less severe or chronic cases, dosage should be one tablet daily for 20-21 consecutive days beginning on Day 5 of menstrual cycle. The tablets are then discontinued for the next 7-8 days. If breakthrough bleeding occurs, the dosage may be increased to 2 or, rarely, 3 tablets daily. Dosage should continue for 3 to 6 cycles.

Dysmenorrhea and Menstrual Irregularities
To achieve maximum effectiveness, Ovral G must be taken as directed and at intervals not exceeding 24 hours. Patients should be instructed to take the tablets at the same time every day, preferably after the evening meals or at bedtime.

During the first cycle of administration, the patient is instructed to take the Ovral G tablet daily for 20-21 consecutive days, beginning on Day 5 of her menstrual cycle. (The first day of bleeding is Day 1). The tablets are then discontinued for the next 7-8 days. Withdrawal bleeding should usually occur within 3 days after the last tablet is taken. The next and all subsequent courses will begin on the 8/9th day after discontinuance, even if withdrawal bleeding has not occurred or is still in progress.

4.3 Contraindications

Ovral G 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 estrogen dependent neoplasia
- Hepatic adenomas or carcinomas, or active liver disease, as long as liver function has not returned to normal
- Undiagnosed vaginal bleeding
- Known or suspected pregnancy
- Hypersensitivity to any of the components of "OVRAL G"

Ovral G is contraindicated for concomitant use with certain anti-viral hepatitis C virus (HCV) medicinal products such as ombitasvir, paritaprevir, ritonavir and dasabuvir (**see section on Special Warnings and Special Precautions for Use; and Interactions**).

4.4 Special Warnings and Special Precautions for Use

Cigarette smoking increases the risk of serious cardiovascular adverse reactions from the use of Ovral G. The 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 Ovral G should be strongly advised not to smoke.

1. VENOUS AND ARTERIAL THROMBOSIS AND THROMBOEMBOLISM

Use of Ovral G is associated with an increased risk of venous and arterial thrombotic and thromboembolic events. Some epidemiological studies suggest that estrogen-progesterone combination with 50 μg or more of ethinyloestradiol may be associated with a higher risk of such events than estrogen-progestin combination with a lower dose of ethinyloestradiol.

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. Minimizing exposure to estrogens and progestins is in keeping good principles of therapeutics.

a. Venous thrombosis and thromboembolism

Use of Ovral G 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 on ocular lesions**.

The use of Ovral G 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 woman-years. Venous thromboembolism is fatal in 1-2% of cases.

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

Examples of predisposing conditions for venous thrombosis and thromboembolism are:

- Certain inherited or acquired thrombophilias (the presence of an inherited thrombophilia may be indicated by a family history of venous thrombotic/thromboembolic events)
- 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 OVRAL G, are listed in **(Section 4.3 Contraindications)**.

If feasible, Ovral G 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, Ovral G should be started no earlier than Day 28 after delivery or second-trimester abortion.

b. Arterial thrombosis and thromboembolism
The use of Ovral G increases the risk of arterial thrombotic and thromboembolic events. Reported events include myocardial infarction and cerebrovascular events (ischemic and hemorrhagic stroke, transient ischemic attack).
The risk of arterial thrombotic and thromboembolic events is further increased in women with underlying risk factors.
Caution must be exercised when prescribing Ovral G for women with risk factors for arterial thrombotic and thromboembolic events.

Examples of risk factors for arterial thrombotic and thromboembolic events are:
- Smoking
- Certain inherited and acquired thrombophilias
- Hypertension
- Hyperlipidemias
- Obesity
- Increasing age

Ovral G users with migraine (particularly migraine with aura) may be at increased risk of stroke. **(see section 4.3 on Contraindications).**

2. OCULAR LESIONS

With use of Ovral G, 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, Ovral G should be discontinued and the cause immediately evaluated.

3. CARCINOMA OF THE REPRODUCTIVE ORGANS

Some studies suggest that Ovral G use may be associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women.

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. 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 Ovral-G compared to never users. The increased risk gradually disappears during the course of the 10 years after cessation of Ovral-G 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 Ovral-G users (due to more regular clinical monitoring), the biological effects of Ovral-G, 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 Ovral-G 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.

4. HEPATIC NEOPLASIA/LIVER DISEASE/HEPATITIS C

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

Women with a history of Ovral G related cholestasis or women with cholestasis during pregnancy are more likely to have this condition with Ovral G use. If these patients receive Ovral G they should be carefully monitored and, if the condition recurs, Ovral G should be discontinued.

Hepatocellular injury has been reported with Ovral G 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 Ovral G and consult their doctor.

HEPATITIS C

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

5. BLOOD PRESSURE

Increases in blood pressure have been reported in women taking Ovral G. In women with hypertension, a history of hypertension or hypertension related diseases (including certain renal diseases), another drug may be preferable. If Ovral-G is used in such cases, close monitoring is recommended and, if a significant increase in blood pressure occurs, Ovral G should be discontinued.

Ovral-G use is contraindicated in women with uncontrolled hypertension. **(see section 4.3 on Contraindications)**.

6. MIGRAINE/HEADACHE

The onset or exacerbation of migraine or development of headache of a new pattern, which is recurrent, persistent, or severe, requires discontinuation of the drug and evaluation of the cause. Women with migraine (particularly migraine with aura) who take Ovral G may be at increased risk of stroke **(see section on 4.3 on Contraindications)**.

PRECAUTIONS

1. GENERAL

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

Diarrhea and/or vomiting may reduce hormone absorption resulting in decreased serum concentrations.

2. PHYSICAL EXAMINATION AND FOLLOW UP

A complete personal and family medical history and physical examination, including blood pressure, should be taken prior to the initiation of Ovral G use. Such medical examinations should be repeated periodically during the use of Ovral G.

3. CARBOHYDRATE AND LIPID EFFECTS

Glucose intolerance has been reported in Ovral G users. Women with impaired glucose tolerance or diabetes mellitus who use Ovral G should be carefully monitored. Persistent hypertriglyceridemia may occur in a small proportion of Ovral G users. Elevations of plasma triglycerides may lead to pancreatitis.

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

4. GENITAL BLEEDING

In some women withdrawal bleeding may not occur during the tablet-free interval. If Ovral G 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.

Breakthrough bleeding/spotting may occur in women taking Ovral G, especially during the first three months of use. If this bleeding persists or recurs nonhormonal causes should be considered and adequate diagnostic measures may be indicated. If pathology

has been excluded, continued use of Ovral G 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

5. DEPRESSION

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

4.5 Interaction with Other Medicaments and Other Forms of Interaction

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 on Contraindications and Special Warnings and Special precautions for use).**

Therefore, Ovral G users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with anti-viral HCV medicinal products such as ombitasvir, paritaprevir, ritonavir, dasabuvir. Ovral G 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 Ovral G.

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)
- Certain antibiotics (e.g., ampicillin and other penicillins, tetracyclines), by a decrease of enterohepatic circulation of estrogens

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 Ovral G

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 Ovral G has been reported to increase the risk of galactorrhea.

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)

4.6 Pregnancy and Lactation

Extensive epidemiological studies have revealed no increased risk of birth defects in children born to women who used Ovral G prior to pregnancy.
Studies do not suggest a teratogenic effect; particularly insofar as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy. **(See also section 4.3 on Contraindications)**.

Small amounts of estrogens and progestones 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 influenced by Ovral G as they may reduce the quantity and change the composition of breast milk.

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

4.7 Effects on Ability to Drive and Use Machines

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

4.8 Adverse Reactions

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 Ovral G has been associated with:

• An increased risk of arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, transient ischemic attack, venous thrombosis and pulmonary embolism.
• An increased risk of cervical intraepithelial neoplasia and cervical cancer
• An increased risk of being diagnosed with breast cancer
• An increased risk of benign hepatic tumors (e.g., focal nodular hyperplasia, hepatic adenoma)

(See also section 4.4 Special Warnings and 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. 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
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
Gastrointestinal disorders	
Common	Nausea; vomiting; abdominal pain
Uncommon	Abdominal cramps; bloating
Very Rare	Pancreatitis; hepatic adenomas; hepatocellular carcinomas, ischemic 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
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	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.
** Ovral G may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.
*** Serum folate levels may be depressed by Ovral G therapy.

4.9 Over dosage

Serious ill effects have not been reported following acute ingestion of large doses of Ovral G by young children.

Overdosage may cause nausea, and withdrawal bleeding may occur in females.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

MODE OF ACTION

The hormonal components of Ovral G inhibit ovulation by suppressing gonadotropin release.

5.2 Pharmacokinetic Properties

Absorption:
Ethinylestradiol and norgestrel 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%. Norgestrel does not undergo first-pass metabolism and is thereby completely bioavailable.

Metabolism:
Norgestrel is extensively plasma protein bound both to sex hormone binding globulin (SHBG) and albumin. Ethinyl estradiol, 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 ethinyl estradiol 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 a 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 norgestrel is approximately 24 hours. The drug is primarily metabolized by reduction of the A ring followed by glucuronidation. About 60% of norgestrel is excreted in the urine and 40% is eliminated in the feces.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

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

6.2 Incompatibilities

None

6.3 Shelf-Life

30 months

6.4 Special Precautions for Storage

Store below 30°C. Protect from light.

6.5 Nature and Contents of Container

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

6.6. Instruction for Use/Handling

Keep out of reach of children.