PRODUCT MONOGRAPH

PrOVIMA® 21 and PrOVIMA® 28

Levonorgestrel and Ethinyl Estradiol Tablets

USP

150 mcg Levonorgestrel and 30 mcg Ethinyl Estradiol Tablets

Oral Contraceptive

APOTEX INC.
150 Signet Drive
Toronto, Ontario
M9L 1T9

Date of Revision:
January 30, 2026

Submission Control No. 304245

Table of Contents

PrOVIMA® 21 and PrOVIMA®28

Levonorgestrel and Ethinyl Estradiol Tablets, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablet, 150 mcg levonorgestrel and 30 mcg ethinyl estradiol	OVIMA 21: Corn starch, crospovidone, lactose monohydrate, magnesium stearate and povidone. OVIMA 28: Corn starch, crospovidone, FD&C Red No. 3 Lake, lactose anhydrous, magnesium stearate and povidone.

INDICATIONS AND CLINICAL USE

OVIMA tablets are indicated for conception control.

Geriatrics (> 65 years of age):
OVIMA is not indicated for use in postmenopausal women.

Pediatrics:
Safety and efficacy of levonorgestrel and ethinyl estradiol tablets have been established in women of reproductive age. Use of this product before menarche is not indicated.

CONTRAINDICATIONS

Combination Oral Contraceptives (COCs) are contraindicated in the following:

- History of or actual thrombophlebitis or thromboembolic disorders
- History of or actual cerebrovascular disorders
- History of or actual myocardial infarction or coronary arterial disease
- Deep vein thrombosis (current or history)
- Thrombogenic valvulopathies and Thrombogenic rhythm disorders
- Hereditary or acquired thrombophilias
- Migraine with focal neurological symptoms such as aura (current or history)
- Active liver disease or abnormal liver function testing
- History of or actual benign or malignant liver tumours
- Known or suspected carcinoma of the breast
- Known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal vaginal bleeding

- Steroid-dependent jaundice, cholestatic jaundice, history of jaundice of pregnancy.
- Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields
- When pregnancy is suspected or diagnosed
- Hypersensitivity to any of the components of OVIMA. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph
- Diabetes with vascular involvement
- Uncontrolled hypertension
- Pancreatitis associated with severe hypertriglyceridemia (current or history)
- Use with the anti-viral Hepatitis C Virus (HCV) combination drug regimen ombitasvir, paritaprevir, ritonavir and dasabuvir, with or without ribavirin (see WARNINGS AND PRECAUTIONS: Hepatic/Biliary/Pancreatic and DRUG INTERACTIONS).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in hormonal contraceptive users older than 35 years of age who smoke. Women should be counselled not to smoke. (see WARNINGS AND PRECAUTIONS: Cardiovascular)

Patients should be counselled that birth control pills **DO NOT PROTECT** against sexually transmitted infections (STIs) including HIV/AIDS. For protection against STIs, it is advisable to use latex or polyurethane condoms **IN COMBINATION WITH** birth control pills.

General

For any estrogen/progestin combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestin that is compatible with a low failure rate and the needs of the individual patient. New users of COCs should be started on preparations containing less than 50 mcg of estrogen.

Discontinue Medication at the Earliest Manifestation of the following:

A. **Thromboembolic and cardiovascular disorders,** such as thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric ischemia, mesenteric thrombosis and retinal thrombosis.

B. **Conditions that predispose to venous stasis and to vascular thrombosis (e.g.** immobilization after accidents or confinement to bed during long-term illness). Other non-hormonal methods of contraception should be used until regular activities are resumed. For use of oral contraceptives when surgery is contemplated, see WARNINGS AND PRECAUTIONS: Peri-Operative Considerations.

C. **Partial or complete loss of vision** (see WARNINGS AND PRECAUTIONS: Ophthalmalogic)

D. **Papilledema or ophthalmic vascular lesions**

E. **Severe headache of unknown etiology, worsening of pre-existing migraine headache**

F. **Increase in epileptic seizures.**

The following information is provided from studies of combination oral contraceptives (COCs).

The use of combination hormonal contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia and gallbladder disease, although the risk of serious morbidity and mortality is small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly if associated with the presence of other risk factors such as hypertension, hyperlipidemias, obesity and diabetes.

Carcinogenesis and Mutagenesis

Breast Cancer

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 currently 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 an earlier detection of breast cancer in COC users, 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.

Increasing age and a strong family history are the most significant risk factors for the development of breast cancer. Other established risk factors include obesity, nulliparity and late age for first full-term pregnancy. The identified groups of women that may be at increased risk of developing breast cancer before menopause are long-term users of COCs (more than eight years) and starters at early age. The use of COCs may accelerate the growth of an existing but undiagnosed breast cancer. Since any potential increased risk related to COC use is small, there is no reason to change prescribing habits at present.

Women receiving COCs should be instructed in self-examination of their breasts. Their physicians should be notified whenever any masses are detected. A yearly clinical breast examination is also recommended, because if a breast cancer should develop, drugs that contain estrogen may cause a rapid progression.

Cervical Cancer

The most important risk factor for cervical cancer is persistent human papillomavirus infection. Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, e.g., cervical screening and sexual behaviour including use of barrier contraceptives

In cases of undiagnosed abnormal genital bleeding adequate diagnostic measures are indicated.

Hepatocellular Carcinoma

OVIMA is contraindicated in patients with a history of or actual benign or malignant liver tumours.

Hepatocellular carcinoma may be associated with oral contraceptives. The risk appears to increase with duration of hormonal contraceptive use. However, the attributable risk (the excess incidence) of liver cancer in oral contraceptive users is extremely small.

See Product Monograph PART II SCIENTIFIC INFORMATION: TOXICOLOGY, Chronic Toxicity for discussion of animal data.

Cardiovascular

Predisposing Factors for Coronary Artery Disease

Cigarette smoking increases the risk of serious cardiovascular side effects and mortality. Birth control pills increase this risk especially with increasing age. Convincing data are available to support an upper age limit of 35 years for oral contraceptive use in women who smoke.

Other women who are independently at high risk for cardiovascular disease include those with diabetes, hypertension, abnormal lipid profile, obesity or a family history of these. Whether COCs accentuate this risk is unclear.

In low risk, non-smoking women of any age, the benefits of oral contraceptive use outweigh the possible cardiovascular risks associated with low dose formulations. Consequently, oral contraceptives may be prescribed for these women up to the age of menopause.

Hypertension

COC use is contraindicated in women with uncontrolled hypertension (see CONTRAINDICATIONS)

Patients with essential hypertension whose blood pressure is well-controlled may be given COCs but only under close supervision. If a significant elevation of blood pressure in previously normotensive or hypertensive subjects occurs at any time during the administration of the drug,

cessation of medication is necessary.

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

Endocrine and Metabolism

Diabetes

Glucose intolerance has been reported in COC users. Current low-dose COCs exert minimal impact on glucose metabolism. Diabetic patients, or those with a family history of diabetes, should be observed closely to detect any worsening of carbohydrate metabolism. Women who are predisposed to diabetes, with impaired glucose tolerance or who have diabetes mellitus should be carefully monitored if using COCs. Young diabetic patients whose disease is of recent origin, well-controlled, and not associated with hypertension or other signs of vascular disease such as ocular fundal changes, should be monitored more frequently while using oral contraceptives.

Lipid and Other Metabolic Effects

A small proportion of women will have adverse lipid changes while taking oral contraceptives. Nonhormonal contraception should be considered in women with uncontrolled dyslipidemias. (See also CONTRAINDICATIONS). Persistent hypertriglyceridemia may occur in a small population of combination oral contraceptive users. Elevations of plasma triglycerides may lead to pancreatitis and other complications.

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

Gastrointestinal

Published epidemiological studies indicate a possible association of COC use and the development of Crohn's disease and ulcerative colitis, although this has not been firmly established.

Absorption

Vomiting and/or diarrhea may reduce absorption of oral contraceptives resulting in decreased serum concentration and therefore may reduce contraceptive efficacy. Physicians should advise the patients of the need for a back-up contraceptive method in the case of such gastrointestinal symptoms.

Genitourinary

Vaginal Bleeding

Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology. See also WARNINGS AND PRECAUTIONS: Sexual Function/Reproduction.

Fibroids

Patients with fibroids (leiomyomata) should be carefully observed. Sudden enlargement, pain, or tenderness requires discontinuation of the use of COCs.

Hematologic

Venous and arterial thrombosis and thromboembolism

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

Venous thrombosis and thromboembolism

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

The use of any combined oral contraceptive carries an increased risk of VTE compared with no use. Reported events include deep venous thrombosis, thrombophlebitis, pulmonary embolism and mesenteric thrombosis. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive. The increased risk is less than the risk of VTE associated with pregnancy, which is estimated as 60 cases per 100,000 women years. VTE is fatal in 1-2% of cases.

Other Risk Factors for Venous Thromboembolism

Other generalized risk factors for venous thromboembolism include but are not limited to a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), severe obesity (body mass index ≥30 kg/m2) and systemic lupus erythematosus. The risk of VTE also increases with age. The risk of VTE may be temporarily increased with prolonged immobilization, major surgery, trauma, recent delivery, or second-trimester abortion. Also, patients with a leg cast should be closely supervised.

If a hereditary or acquired predisposition for venous thromboembolism is suspected, the woman should be referred to a specialist for advice before deciding on any COC use.

Arterial thrombosis and thromboembolism

The use of COCs increases the risk of arterial thrombotic and thromboembolic events. Reported events include myocardial infarction and cerebrovascular events (ischemic and hemorrhagic stroke, transient ischemic attack). For information on retinal vascular thrombosis see WARNINGS AND PRECAUTIONS: Ophthalmologic.

The risk of arterial thrombotic and thromboembolic event is further increased in women with underlying risk factors. Examples of risk factors for arterial thrombotic and thromboembolic events are smoking hypertension, hyperlipidemias, obesity and increasing age. Caution must be exercised when prescribing COCs for women with risk factors for arterial thrombotic and thromboembolic events.

Hepatic/Biliary/Pancreatic

Hepatic Function

OVIMA is contraindicated in patients with active liver disease or abnormal liver function testing (see CONTRAINDICATIONS and DRUG INTERACTIONS: Drug-Laboratory Test Interactions).

Acute or chronic disturbances of liver function necessitate the discontinuation of COC use until markers of liver function return to normal.

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.

Hepatitis C

During clinical trials with patients treated for HCV infections with the combination of ombitasvir, paritaprevir, ritonavir and dasabuvir with or without ribavirin, it was found that transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinyl estradiol-containing medications such as COCs. Therefore OVIMA 21 and OVIMA 28 are contraindicated in hepatitis C patients during treatment with these drugs (see CONTRAINDICATIONS and DRUG INTERACTIONS).

Gallbladder Disease

For women with symptomatic gall bladder disease, consideration should be given to whether the benefits of COCs outweigh the risks. COC use these patients may worsen existing disease.

Jaundice

Patients who have had jaundice, should be given oral contraceptives only with great care and under close observation. Oral contraceptive-related cholestasis has been described in women with a history of pregnancy-related cholestasis. Women with a history of cholestasis may have the condition recur with subsequent hormonal contraceptive use, and in this instance, OVIMA should be discontinued.

The development of severe generalized pruritus or icterus requires that the medication be

withdrawn until the problem is resolved.

If a patient develops jaundice that proves to be cholestatic in type, the use of oral contraceptives should not be resumed. In patients taking hormonal contraceptives, changes in the composition of the bile may occur and an increased incidence of gallstones has been reported.

Hepatic Nodules

Hepatic nodules (adenoma and focal nodular hyperplasia) have been reported, particularly in long-term users of oral contraceptives. Although these lesions are extremely rare, they have caused fatal intra-abdominal hemorrhage and should be considered in women presenting with an abdominal mass, acute abdominal pain, or evidence of intra-abdominal bleeding.

Pancreatic Function

Please see WARNINGS AND PRECAUTIONS: Endocrine and Metabolism: Lipid and Other Metabolic Effects.

Immune

Angioedema

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

Neurologic

Migraine and Headache

The onset or exacerbation of migraine or the development of headache of a new pattern that is recurrent, persistent or severe, requires discontinuation of COCs and evaluation of the cause. (see CONTRAINDICATIONS)

Women with migraine headaches who take oral contraceptives may be at increased risk of stroke. (see CONTRAINDICATIONS)

Ophthalmologic

Patients who are pregnant or are taking oral contraceptives may experience corneal edema that may cause visual disturbances and changes in tolerance to contact lenses, especially of the rigid type. Soft contact lenses usually do not cause disturbances. If visual changes or alterations in tolerance to contact lenses occur, temporary or permanent cessation of wear may be advised.

With use of oral contraceptives 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 oral contraceptives should be discontinued and the cause immediately evaluated.

Peri-Operative Considerations

Thromboembolic Complications - Post-surgery

There is an increased risk of thromboembolic complications in oral contraceptive users after major surgery. If feasible, oral contraceptives should be discontinued and an alternative method substituted at least one month prior to **major** elective surgery and during periods of prolonged immobilization. Oral contraceptive use should not be resumed for at least two weeks after major elective surgery, and only after the first menstrual period has occurred following hospital discharge.

Psychiatric

Patients with a history of emotional disturbances, especially the depressive type, may be more prone to have a recurrence of depression while taking oral contraceptives. Women with a history of depression who use oral contraceptives should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug-related. Women with premenstrual syndrome (PMS) may have a varied response to oral contraceptives, ranging from symptomatic improvement to worsening of the condition.

Renal

Fluid Retention

Hormonal contraceptives may cause some degree of fluid retention.

Sexual Function/Reproduction

Return to Fertility

After discontinuing oral contraceptives therapy, the patient should delay pregnancy until at least one normal spontaneous menstrual cycle has occurred in order to date the pregnancy. An alternate contraceptive method should be used during this time.

Vaginal Bleeding

Breakthrough bleeding/spotting may occur in women taking COCs, 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 to rule out pregnancy, infection, malignancy, or other conditions. Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology. If pathology has been excluded (see WARNINGS AND PRECAUTIONS: Cervical Cancer), continued use of the COC or a change to another formulation may solve the problem.

Amenorrhea

In some women, withdrawal bleeding may not occur during the tablet-free interval. If the COC has been taken according to directions, it is unlikely that the woman is pregnant. However, 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 non-hormonal back-up method of contraception should be used until the possibility of pregnancy is excluded. Pregnancy must be ruled out before COC use is continued.

Women having a history of oligomenorrhea, secondary amenorrhea, or irregular cycles may remain anovulatory or become amenorrheic following discontinuation of estrogen-progestin combination therapy.

Amenorrhea, especially if associated with breast secretion, that continues for six months or more after withdrawal, warrants a careful assessment of hypothalamic-pituitary function.

Reduced Efficacy

The efficacy of COCs may be reduced in the event of missed tablets, gastro-intestinal disturbances or concomitant medication (see DRUG INTERACTIONS).

Skin

Chloasma may occasionally occur with use of hormonal contraceptives, especially in women with a history of chloasma gravidarum. Women with a tendency to develop chloasma should avoid exposure to the sun or ultraviolet radiation while taking hormonal contraceptives.

Special Populations

Pregnant Women

Oral contraceptives should not be taken by pregnant women. If pregnancy occurs during treatment with OVIMA, further intake should be stopped. However, if conception accidentally occurs while taking the pill, there is no conclusive evidence that the estrogen and progestin contained in the oral contraceptive will damage the developing child.

Nursing Women

In breast-feeding women, the use of oral contraceptives results in the hormonal components being excreted in breast milk and may reduce its quantity and quality. Published studies have indicated that during lactation, 0.1% of the daily maternal dose of levonorgestrel and 0.02% of the daily maternal dose of ethinyl estradiol could be transferred to the newborn via milk.

Adverse effects on the child have been reported, including jaundice and breast enlargement. The nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

Pediatrics (<16 years of age)

Safety and efficacy of levonorgestrel and ethinyl estradiol tablets have been established in women of reproductive age. Use of this product before menarche is not indicated.

Geriatrics (> 65 years of age):

OVIMA is not indicated for use in postmenopausal women.

Monitoring and Laboratory Tests

Physical Examination and Follow up

Before oral contraceptives are used, a thorough individual and family history and physical examination should be performed, including a blood pressure determination. In addition, disturbances of the clotting system must be ruled out if any members of the family have suffered from thromboembolic diseases (e.g., deep vein thrombosis, stroke, myocardial infarction) at a young age. Breasts, liver, extremities and pelvic organs should be examined and a Papanicolaou (PAP) smear should be taken if the patient has been sexually active or if it is otherwise indicated.

The first follow-up visit should be done three months after oral contraceptives are prescribed. Thereafter, examinations should be performed at least once a year, or more frequently if indicated. At each annual visit, examination should include those procedures that were done at the initial visit as outlined above or per recommendations of the Canadian Task Force on the Preventive Health Care.

Tissue Specimens
Pathologists should be advised of COC therapy when specimens obtained from surgical procedures and Pap smears are submitted for examination.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

An increased risk of the following serious adverse reactions has been associated with the use of Combined Oral Contraceptives:

- Arterial thromboembolism
- Being diagnosed with breast cancer
- Benign hepatic tumours (e.g. focal nodular hyperplasia, hepatic adenomas)
- Cerebral hemorrhage
- Cerebral thrombosis
- Cervical cancer
- Cervical intraepithelial neoplasia
- Gallbladder disease, including gallstones*
- Hepatocellular carcinomas
- Hypertension
- Inflammatory bowel disease (Crohn's Disease, ulcerative colitis)
- Mesenteric thrombosis
- Myocardial infarction
- Neuro-ocular lesions (e.g. retinal thrombosis)
- Pulmonary embolism
- Stroke
- Transient ischemic attack
- Thrombophlebitis
- Venous thrombosis

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

The following adverse reactions also have been reported in patients receiving COCs: Nausea and vomiting, usually the most common adverse reaction, occurs in approximately 10 percent or

fewer of patients during the first cycle. Other reactions, as a general rule, are seen less frequently or only occasionally.
The following adverse reactions have been reported in patients receiving COC and are believed to be drug related:

- Amenorrhea
- Breakthrough bleeding
- Breast changes: pain, tenderness, enlargement, and secretion
- Change in cervical ectropion and secretion
- Change in corneal curvature (steepening)
- Change in menstrual flow
- Change in weight (increase or decrease)
- Chloasma (melasma) which may persist
- Cholestatic jaundice
- Diminution in lactation when given immediately postpartum
- Dysmenorrhea
- Fluid retention/Edema
- Gastrointestinal symptoms (such as abdominal pain, cramps and bloating)
- Headache, including migraines
- Hepatocellular injury (e.g. hepatitis, hepatic function abnormal)
- Intolerance to contact lenses
- Mood changes, including depression
- Rash (allergic)
- Reduced tolerance to carbohydrates
- Retinal vascular thrombosis
- Spotting
- Temporary infertility after discontinuance of treatment
- Vaginitis including candidiasis

The following adverse reactions have been reported in users of COCs and the association has been neither confirmed nor refuted:

- Acne
- Aggravation of varicose veins
- Anaphylactic (anaphylactoid reactions, including very rare cases of urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms)
- Budd-Chiari syndrome
- Cataracts
- Cerebral-Vascular disease with mitral valve prolapse
- Changes in appetite (increase or decrease)
- Changes in libido
- Changes in Serum Lipid levels, including hypertriglyceridemia
- Colitis
- Congenital anomalies
- Cystitis-like syndrome
- Decrease in serum folate levels**
- Dizziness
- Erythema multiforme
- Erythema nodosum

- Exacerbation of chorea
- Exacerbation of porphyria
- Exacerbation of systemic lupus erythematosus
- Hemolytic uremic syndrome
- Hemorrhagic eruption
- Hepatocellular Carcinomas
- Hirsutism
- Impaired renal function
- Ischemic colitis
- Loss of scalp hair
- Lupus-like syndromes
- Nervousness
- Optic neuritis***
- Pancreatitis
- Premenstrual syndrome
- Sickle-cell disease
- Vaginitis

**Serum folate levels may be depressed by COC therapy.
***Optic neuritis may lead to partial or complete loss of vision.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The contraceptive efficacy and safety of 150 mcg of levonorgestrel and 30 mcg of ethinyl estradiol has been evaluated in a multi-centre study conducted by 17 investigators.

A total of 1,084 subjects, 61.5% of proven fertility, completed 8,186 cycles over 23 months of use with 150 mcg of levonorgestrel and 30 mcg of ethinyl estradiol: 624 completed 6 cycles, 283 completed 12 cycles, 68 completed 18 cycles and 6 completed 23 cycles.

The side effects reported were those commonly associated with oral contraceptives and are listed by the percentage of their occurrence by cycle (see ADVERSE REACTIONS: Clinical Trial Adverse Drug Reactions: Table 1). The most frequent side effects noted were spotting (8.6%), breakthrough bleeding (6.9%), simple headache (5.5%), dysmenorrhea (3.4%), GI symptoms (2.3%), acne (2.0%), nausea (1.9%), breast discomfort (1.8%), vaginal discharge (1.3%), appetite increase (1.1%), and depression (1.1%). These symptoms were usually mild and decreased with time on therapy.

TABLE 1- SIDE EFFECTS BY PERCENTAGE IN LEVONORGESTREL AND ETHINYL ESTRADIOL TREATED PATIENTS

NO. ENROLLED 1084	CYCLE 1	CYCLE 2	CYCLE 3	CYCLE 6	CYCLE 12	CYCLE 18	CYCLE 20	TOTAL CYCLES 8186
Acne	5.5	3.1	2.4	1.6	1.4	---	---	2.0
Allergic Rash	0.2	0.3	---	---	0.4	---	---	0.1
Appetite Decrease	0.7	0.3	0.3	0.6	---	---	---	0.3
Appetite Increase	2.1	1.2	1.7	1.4	0.4	---	---	1.1
Backache	2.1	1.4	1.5	0.3	0.4	---	---	1.0
Breakthrough Bleeding	10.1	8.5	7.6	5.6	4.6	2.9	2.6	6.9
Breast Discomfort	4.0	2.4	2.4	1 .0	2.1	---	---	1.8
Breast Enlargement	2.0	0.7	0.7	0.5	0.4	---	---	0.6
Breast Secretion	0.2	0.2	---	0.3	---	---	---	0.1
Chloasma or Melasma	---	0.1	0.1	---	---	---	---	0.1
Depression	2.0	1.3	0.6	1.1	1.4	1.5	---	1.1
Dizziness	1.1	1.1	0.8	0.6	0.7	---	---	0.5
Dysmenorrhea	6.3	3.5	4.3	2.4	2.8	1.5	---	3.4
Dyspareunia	0.5	0.3	0.2	---	---	---	---	0.1
Edema	0.9	0.1	0.1	1.0	0.4	---	---	0.4
Fatigue	2.0	0.7	1.6	0.5	0.4	---	---	0.9
G.I. Symptoms	5.6	2.9	3.4	1.8	1.4	---	---	2.3
Headache Migraine	1.2	0.5	0.3	0.5	---	1.5	2.6	0.5
Headache Simple	9.6	5.4	5.8	4.8	4.6	8.8	7.9	5.5
Hirsutism	0.3	---	---	---	---	---	---	---
Itching	1.4	0.3	0.7	0.6	0.4	---	---	0.6
Leg Cramps	1.5	0.4	0.6	0.5	---	---	2.6	0.4
Libido Decrease	0.9	1.2	1.2	0.5	0.4	---	---	0.7
Libido Increase	0.6	0.1	0.2	---	---	---	---	0.2
Loss of Scalp Hair	---	0.1	0.2	---	---	---	---	---
Nausea	6.9	2.1	1.3	0.8	2.1	1.5	---	1.9
Nervousness	1.8	0.7	0.6	0.6	0.4	---	---	0.7
Spotting	16.2	10.6	8.4	7.5	5.3	4.4	2.6	8.6
Vaginal Discharge	1.8	1.1	1.9	1.9	2.1	---	---	1.3
Vomiting	1.0	0.5	0.6	0.2	---	1.5	---	0.4

Of 1,084 subjects who completed one cycle, 128 (11.8%) discontinued therapy for medical reasons including breakthrough bleeding 25, simple headache 15, acne 5, amenorrhea 4, depression 10, GI symptoms 5, migraine headache 4, libido decrease 5, nausea 7, nervousness 4, spotting 8, and weight increase 5. Two subjects each dropped out for chloasma or melasma, dizziness, fatigue, leg cramps, and multiple common complaints, and one subject each for allergic rash, breast enlargement, change in amount of flow, change in cycle regularity, edema, hirsutism, loss of libido, loss of scalp hair, and vomiting.

As levonorgestrel and ethinyl estradiol tablets are a reduced dosage formulation of the marketed product 250 mcg of levonorgestrel and 50 mcg of ethinyl estradiol, only routine clinical laboratory safety studies were run. No significant weight or blood pressure changes occurred during the use of levonorgestrel and ethinyl estradiol tablets.

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory results were generally within normal range with no clinically significant differences from laboratory values registered pretreatment (see ADVERSE REACTIONS: Abnormal Hematologic and Clinical Chemistry Findings: Table 2).

TABLE 2

LABORATORY VALUES						
	Pretreatment (Percentage)			Treatment (Percentage)		
INDEX	**Low**	**Normal**	**High**	**Low**	**Normal**	**High**
HEMATOLOGY						
Hemoglobin	5.8	89.3	5.0	1.7	92.2	6.1
Hematocrit	12.8	86.8	0.4	9.1	90.5	0.4
RBC	16.1	82.0	1.9	13.2	84.4	2.4
WBC	6.4	88.7	5.0	7.0	88.1	4.9
Platelets	-	89.1	10.9	3.6	89.3	7.1
BIOCHEMISTRY						
Tot. Protein	-	94.4	5.6	-	98.3	1.7
Albumin	0.4	99.6	-	0.9	99.1	-
Cholesterol	13.1	85.8	1.1	2.8	97.2	-
BUN	19.3	80.7	-	8.9	91.1	-
PROFILE LIVER						
Tot. Bilirubin	-	97.2	2.8	0.6	98.1	1.3

LABORATORY VALUES						
	Pretreatment (Percentage)			Treatment (Percentage)		
INDEX	**Low**	**Normal**	**High**	**Low**	**Normal**	**High**
SGOT	3.9	93.5	2.5	-	97.3	2.7
SGPT	5.6	92.7	1.6	1.7	98.3	-
Alk. Phosphatase	1.8	89.1	9.2	1.3	98.7	-
URINALYSIS						
Spec. Gravity	0.5	96.1	3.4	0.7	95.1	4.3
pH	2.6	93.0	4.4	1.6	93.9	4.6
Urine Albumin	-	98.8	1.2	-	99.2	0.8
Urine Glucose	-	99.8	0.2	-	99.7	0.3

Cervical cytology determinations were within normal limits, except for seven pretreatment and six during treatment cervical cytology smears which were all Class III (see ADVERSE REACTIONS: Abnormal Hematologic and Clinical Chemistry Findings: Table 3). Subsequent PAP smears done in all subjects but one were normal. During the course of the study, eleven cervical biopsies from ten subjects were reported. All eleven biopsies were benign with no evidence of malignancy.

TABLE 3
PAP SMEAR BY CLASS

	Pretreatment			During Treatment		
CLASS	**I**	**II**	**III-V**	**I**	**II**	**III-V**
No.	926	71	7	681	79	6
Percentage	(92.2%)	(7.1%)	(0.7%)	(88.9%)	(10.3%)	(0.8%)

Endometrial biopsies were performed by one investigator on eleven subjects during the first 12 cycles of levonorgestrel and ethinyl estradiol tablets . All endometrial samples were the suppressed type of healthy, inactive, asynchronous endometrium not supportive of nidation.

Physical examinations conducted pretreatment and regularly throughout the course of treatment completed the safety aspect of the investigation. These examinations revealed breast masses (4), convulsive disorder (1), cystitis (11), gall bladder disease (1), hemorrhagic diathesis (3), kidney disease (1), vaginal infection (25), varicosities (1), and venereal disease (4).

DRUG INTERACTIONS

Overview

The concurrent administration of COCs with other substances may result in an altered response to either agent. Decreased ethinyl estradiol (EE) serum concentration 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 concentration, 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 ethinyl estradiol tablets. 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 led 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.

Reduced effectiveness of the COC, should it occur, is more likely with the low-dose formulations. It is important to ascertain all drugs that a patient is taking, both prescription and non-prescription, before COCs are prescribed.

Examples of substances that may decrease serum EE concentrations:

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

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 acetaminophen.
- Substances that inhibit cytochrome P 450 3A4 isoenzymes such as indinavir, fluconazole and troleandomycin.
- Troleandomycin may increase the risk of intrahepatic cholestasis during coadministration with COCs.

Ethinyl estradiol 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 (eg, cyclosporine, theophylline, corticosteroids) or decreased (eg, 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).

Concomitant use with the combination drug regimen ombitasvir, paritaprevir, ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS: Hepatic/Biliary/Pancreatic). Therefore, COC 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 drug combinations such as ombitasvir, paritaprevir, ritonavir, and dasabuvir with or without ribavirin. COCs can be restarted 2 weeks following completion of treatment with an anti-viral HCV medicinal product.

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

For possible drug interactions with COCs, see DRUG INTERACTIONS: Drug-Drug Interactions: Tables 4 and 5.

Drug-Drug Interactions

Table 4*: Drugs That May Decrease the Efficacy of Oral Contraceptives

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Antibiotics	Ampicillin Penicillin	intestinal hurry.	For short course, use additional method or use another drug. For long course, use another method.
	Cotrimoxazole	Enterohepatic circulation disturbance, intestinal hurry.	For short course, use additional method or use another drug. For long course, use another method.
	Rifabutin Rifampin	Increased metabolism of progestins. Suspected acceleration of estrogen metabolism.	Use another method.
	Chloramphenicol Metronidazole Neomycin Nitrofurantoin Sulfonamide Tetracyclines	Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation, except for tetracyclines.	For short course, use additional method or use another drug. For long course, use another method.
	Troleandomycin	May retard metabolism of OCs, increasing the risk of cholestatic jaundice.	
Anticonvulsants	Carbamazepine Ethosuximide Felbamate Lamotrigine Oxcarbazine Phenobarbital	Induction of hepatic microsomal enzymes. Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG.	Use higher dose OCs (50 mcg ethinyl estradiol), another drug or another method.

Table 4*: Drugs That May Decrease the Efficacy of Oral Contraceptives			
Class of Compound	**Drug**	**Proposed Mechanism**	**Suggested Management**
	Phenytoin Primidone Topiramate		
Antifungals	Griseofulvin	Stimulation of hepatic metabolism of contraceptive sterioids may occur.	Use another method.
Cholesterol Lowering Agents	Clofibrate	Reduces elevated serum triglycerides and cholesterol.; this reduces OC efficacy	Use another method.
HIV Protease Inhibitors	Ritonavir	Induction of hepatic microsomal enzymes.	Use another drug or another method.
Non-nucleoside reverse transcriptase inhibitors	Nevirapine	Induction of hepatic microsomal enzymes	Use another drug or another method.
Sedatives and Hypnotics	Benzodiazepines Barbiturates Chloral Hydrate Glutethimide Meprobamate	Induction of hepatic microsomal enzymes.	For short course, use additional method or another drug. For long course, use another method or higher dose OCs.
Antacids		Decreased intestinal absorption of progestins.	Dose two hours apart
Other Drugs	Phenylbutazone** Antihistamines ** Analgesics** Antimigraine Preparations** Vitamin E	Reduced OC efficacy has been reported. Remains to be confirmed.	

*Adapted from Dickey, RP, ed.: Managing Contraceptive Pill Patients, 5th edition Creative Informatics Inc., Durant, OK, 1987

** Refer to Oral Contraceptives 1994, A Report by the Special Advisory Committee on Reproductive Physiology to the Drugs Directorate, Health Protection Branch, Health Canada

Table 5*: Modification of Other Drug Action by Oral Contraceptives			
Class of Compound	**Drug**	**Proposed Mechanism**	**Suggested Management**
Alcohol		Possible increased levels of ethanol or acetaldehyde.	Use with caution.
Alpha-II Adrenoreceptor Agents	Clonidine	Sedation effect increased.	Use with caution.
Anticoagulants	All	OCs increase clotting factors, decrease efficacy. However, OCs may potentiate action in some patients.	Use another method.
Anticonvulsants	All	Estrogens may increase risk of	Use another method.

Table 5*: Modification of Other Drug Action by Oral Contraceptives			
Class of Compound	**Drug**	**Proposed Mechanism**	**Suggested Management**
		seizures	
	Lamotrigine	Decrease lamotrigine levels, may lead to breakthrough seizures.	Use another method.
Antidiabetic Drugs	Oral Hypoglycemics and Insulin	OCs may impair glucose tolerance. and increase blood glucose.	Use low-dose estrogen and progestin OC or another method. Monitor blood glucose.
Antihypertensive Agents	Guanethidine and Methyldopa	Estrogen component causes sodium retention, progestin has no effect.	Use low-dose estrogen OC or use another method.
	Beta Blockers	Increased drug effect (decreased metabolism)	Adjust dose of drug if necessary. Monitor cardiovascular status.
Antipyretics	Acetaminophen	Increased metabolism and renal clearance.	Dose of drug may have to be increased.
	Antipyrine	Impaired metabolism.	Decrease dose of drug.
	ASA	Effects of ASA may be decreased by the short-term use of OCs.	Patients on chronic ASA therapy may require an increase in ASA dosage.
Anti-viral hepatitis C virus	Ombitasvir Paritaprevir Ritonavir Dasabuvir	May increase the risk of ALT elevations	Concomitant use is contraindicated (see CONTAINDICATIONS).
Aminocaproic Acid		Theoretically, a hypercoagulable state may occur because OCs augment clotting factors.	Avoid concomitant use.
Betamimetic Agents	Isoproterenol	Estrogen causes decreased response to these drugs.	Adjust dose of drug as necessary. Discontinuing OCs can result in excessive drug activity.
Caffeine		The actions of caffeine may be enhanced as OCs may impair the hepatic metabolism of caffeine	Use with caution.
Cholesterol-lowering Agents	Clofibrate	Their action may be antagonized by OCs. OCs may also increase metabolism of clofibrate.	May need to increase dose of clofibrate.
Corticosteroids	Prednisone	Markedly increases serum levels.	Possible need for decrease in dose.
Cyclosporine		May lead to an increase in cyclosporine levels and hepatoxicity.	Monitor hepatic function. The cyclosporine dose may have to be decreased.
Folic Acid		OCs have been reported to impair folate metabolism.	May need to increase dietary intake, or supplement.
Meperidine		Possible increased analgesia and CNS depression due to decreased metabolism of meperidine.	Use combination with caution.
Phenothiazine Tranquilizers	All phenothiazines, Reserpine, and similar drugs.	Estrogen potentiates the hyperprolactinemia effect of these drugs.	Use other drugs or lower dose OCs. If galactorrhea or hyperprolactinemia occurs, use other method.
Sedatives and	Chlordiazepoxide	Increased effect (increased	Use with caution

Table 5*: Modification of Other Drug Action by Oral Contraceptives			
Class of Compound	**Drug**	**Proposed Mechanism**	**Suggested Management**
Hypnotics	Lorazepam Oxazepam Diazepam	metabolism)	
Theophylline	All	Decreased oxidation, leading to possible toxicity.	Use with caution. Monitor theophylline levels.
Tricyclic Antidepressants	Clomipramine (possibly others)	Increased side effects: i.e., depression. Increased serum levels due to decreased clearance.	Use with caution.
Vitamin B_{12}		OCs have been reported to reduce serum levels of Vitamin B_{12}.	May need to increase dietary intake, or supplement.

*Adapted from Dickey, RP, ed.: Managing Contraceptive Pill Patients, 5th edition Creative Informatics Inc., Durant, OK, 1987

Several of the anti-HIV protease inhibitors (eg, ritonavir) and non-nucleoside reverse transcriptase inhibitors (eg, nevirapine) have been studied with coadministration of oral combination hormonal contraceptives; significant changes (increase and decrease) in the mean AUC of the estrogen and progestogen and the potential to affect hepatic metabolism have been noted in some cases. The efficacy and safety of oral contraceptive products may be affected. Healthcare providers should refer to the label of the individual anti-HIV protease inhibitor for further drug-drug interaction information.

Drug-Food Interactions

No data is available.

Drug-Herb Interactions

Herbal products containing St. John's Wort (hypericum perforatum) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

Drug-Laboratory Interactions

Results of laboratory tests should be interpreted in the light that the patient is on COCs. The following laboratory tests are modified:

Liver Function Tests	
Bromsulphthalein Retention Test (BSP)	Moderate increase
AST (SGOT) and GGT	Minor increase
Alkaline Phosphatase	Variable increase
Serum Bilirubin	Increased, particularly in conditions predisposing to or associated with hyperbilirubinemia
Coagulation Tests	
Factors II, VII, IX, X, XII and XIII	Increased
Factor VIII	Mild increase

Platelet aggregation and adhesiveness	Mild increase in response to common aggregating agents
Fibrinogen	Increased
Plasminogen	Mild increase
Antithrombin III	Mild decrease
Prothrombin Time	Decreased
Thyroid Function Tests	
Protein-bound Iodine (PBI)	Increased
Total Serum Thyroxine (T_3 andT4)	Increased
Thyroid Stimulating Hormone (TSH)	Unchanged
Free T3 Resin Uptake	Decreased
Adrenocortical Function Tests	
Plasma Cortisol	Increased
Cortisol Binding Globulin	Increased
Dehydroepiandrosterone sulfate (DHEAS)	Decreased
Miscellaneous Tests	
Serum Folate	Occasionally decreased
Glucose Tolerance Test	Variable decrease with return to normal after 6 to 12 months
Insulin Response	Mild-to moderate-decrease
c-Peptide Response	Mild-to moderate decrease

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

OVIMA 21 TABLETS REGIMEN

Each cycle consists of 21 days on medication and a 7-day interval without medication (three weeks on, one week off).

The dosage of OVIMA tablets is one tablet daily for 21 consecutive days per menstrual cycle, according to prescribed schedule.

For the first cycle of medication, the patient is instructed to take one OVIMA tablet daily for 21 consecutive days beginning on Day 1 of her menstrual cycle, on Day 5, or on the first Sunday after her period begins. (For the first cycle only, the first day of menstrual flow is considered Day 1.) The tablets are then discontinued for seven days (one week). Withdrawal bleeding should usually occur within three days following discontinuation of OVIMA.

The patient begins her next and all subsequent 21-day courses of OVIMA tablets (following the same 21 days on, 7 days off) on the same day of the week that she began her first course. She begins taking her tablets seven days after discontinuation, regardless of whether or not withdrawal bleeding is still in progress.

OVIMA 28 TABLETS REGIMEN

Each cycle consists of 21 days of white OVIMA tablets (active tablets) followed by 7 days of pink inert tablets (three weeks on OVIMA, one week on inert tablets).

The dosage of OVIMA tablets is one tablet daily for 21 consecutive days per menstrual cycle, according to prescribed schedule, followed by one inert tablet daily for 7 consecutive days according to prescribed schedule.

For the first cycle of medication, the patient is instructed to take one white tablet daily for 21 consecutive days beginning on Day 1 of her menstrual cycle, on Day 5, or on the first Sunday after her period begins. (For the first cycle only, the first day of menstrual flow is considered Day 1.) One pink tablet is taken daily for the following seven consecutive days. Withdrawal bleeding should usually occur within three days following the discontinuation of white OVIMA tablets, i.e., during the week the patient is taking the pink inert tablets. The patient begins her next and all subsequent 28-day courses of tablets on the same day of the week that she began her first course. She continues her next course of 28 tablets immediately after the last course, regardless of whether or not a period of withdrawal bleeding is still in progress. There is no need for the patient to count days between cycles because there are no "off-tablet days".

Missed Dose

The patient should be instructed to use the following chart if she misses one or more of her birth control pills. She should be told to match the number of pills with the appropriate starting time for her type of pill.

SUNDAY START	OTHER THAN SUNDAY START
Miss One Pill	**Miss One Pill**
Take it as soon as you remember, and take the next pill at the usual time. This means that you might take two pills in one day.	Take it as soon as you remember, and take the next pill at the usual time. This means that you might take two pills in one day.
Miss Two Pills in a Row	**Miss Two Pills in a Row**
First two weeks 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. **Third week** 1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of	**First two weeks** 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. **Third week** 1. Safely dispose of the rest of the pill pack and start a new pack that same day.

the pack and start a new pack that day. 3. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**	2. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**
Miss Three or More Pills in a Row	**Miss Three or More Pills in a Row**
Anytime in the cycle 1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. **If You Miss Two periods in a Row, Call Your Doctor or Clinic.**	**Anytime in the cycle** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**

Contraceptive reliability may be reduced if active tablets are missed and particularly if the missed tablets extend the tablet-free interval. If active tablets were missed and intercourse took place in the week before the tablets were missed, the possibility of pregnancy should be considered.

Administration

Tablets for oral use.

SPECIAL NOTES ON ADMINISTRATION

Administration
It is recommended that OVIMA tablets be taken at the same time each day, preferably after the evening meal or at bedtime.

OVIMA is effective from the first day of therapy if the tablets are begun as described under "DOSAGE AND ADMINISTRATION".

If OVIMA tablets administration is initiated postpartum (no earlier than day 28 after delivery in the nonlactating mother) or after Day 1 of the first menstrual cycle of medication, contraceptive reliance should not be placed on OVIMA until after the first seven consecutive days of administration. The possibility of ovulation and conception prior to initiation of medication should be considered. Therefore, nonhormonal methods of contraception (such as condoms and spermicide) should be used for the first 7 days of tablet taking.

If spotting or breakthrough bleeding occurs, the patient is instructed to continue on the same regimen. This type of bleeding usually is transient and without significance; however, if the bleeding is persistent or prolonged, the patient is advised to consult her physician.

The patient should be instructed to use the following chart if she misses one or more of her birth control pills. She should be told to match the number of pills with the appropriate starting time for her type of pill.

Advice in case of vomiting and/or diarrhea

If vomiting and/or diarrhea occurs within 4 hours after tablet-taking, tablet absorption may be incomplete. In such event, advice concerning the Management of Missed Tablet is outlined in the above chart. The woman must take the extra active tablet(s) needed from a backup pack.

No hormonal contraceptive use (in the past month)

Tablet-taking should start on day 1 of the woman's natural cycle (ie, the first day of her menstrual bleeding). Starting on days 2 to 7 is allowed, but for the first 7 days of tablet-taking during the first cycle, a nonhormonal back-up method of birth control (such as condoms and spermicide) is recommended.

Changing from another COC pill

The woman should start OVIMA preferably on the day after the last active tablet of her previous COC, but at the latest, on the day following the usual tablet-free or inactive tablet interval of her previous COC.

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

The woman may switch any day from the progestin-only pill and should begin OVIMA the next day. She should start OVIMA on the day that a progestin-only implant or a progestin--only IUD is removed. OVIMA use should begin on the day that the next progestin-only injection is scheduled. In all of these situations, the woman should be advised to use a nonhormonal back-up method for the first 7 days of tablet-taking.

Following first-trimester abortion

The woman may start OVIMA immediately. Additional contraceptive measures are not needed.

Following delivery or second-trimester abortion

Since the immediate post-partum period is associated with an increased risk of

thromboembolism, COCs should be started no earlier than day 28 after delivery in the nonlactating mother or after second-trimester abortion. The woman should be advised to use a nonhormonal back-up method for the first 7 days of tablet-taking. However, if intercourse has already occurred, the possibility of pregnancy should be ruled out before the actual start of COC use or the woman must wait for her first menstrual period.

OVERDOSAGE

Symptoms of COC 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.

For management of suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Oral Contraception:

Levonorgestrel and ethinyl estradiol tablets acts primarily through the mechanism of gonadotropin suppression due to estrogenic and progestational activity of their components, in a manner that inhibits ovulation, which leads to contraception. Some studies have demonstrated changes in the endometrium and cervical mucus with the use of hormonal contraceptives. However, further research is required to determine, quantitatively, whether or not the contribution of changes in endometrium and cervical mucus, observed with combination oral contraceptives, have a role in the prevention of pregnancy.

Progestogens can have, in addition to progestational activity, estrogenic, anti-estrogenic and androgenic activity. When combined with estrogen, the progestogen will markedly affect the overall biological activity by producing a synergistic, summative or diminutional effect on activity. Comparisons of progestogen potency are not considered scientifically valid because the effects of one progestogen cannot be directly compared with those of another.[28]

A study of serum luteinizing hormone (LH), follicle stimulating hormone (FSH), progesterone and 17β-estradiol in patients taking 150 mcg d-norgestrel (as the dl-racemate) plus 30 mcg ethinyl estradiol indicated reduction or abolition of the mid-cycle ovulatory peak and post-ovulatory levels commonly associated with these hormones and gonadotrophins respectively. (For plasma progesterone determinations while on levonorgestrel and ethinyl estradiol tablets of ethinyl estradiol, see CLINICAL TRIALS).

Endometrial biopsies taken during the course of therapy with 250 mcg d-norgestrel (as the dl-racemate) plus 50 mcg ethinyl estradiol revealed a histological sequence in the menstrual cycle of early glandular epithelial stimulation followed by later inhibition after the first half of the menstrual cycle. (For endometrial biopsy results with levonorgestrel and ethinyl estradiol

tablets, see CLINICAL TRIALS).

Cervical mucus studies with 250 mcg d-norgestrel (as the dl-racemate) plus 50 mcg ethinyl estradiol, and 37.5 mcg d-norgestrel (as the dl-racemate) revealed absence of ferning and decreased spinnbarkeit, indicative of poor conditions for sperm penetration and migration.

The results of assays for prolactin in a group of 11 normally ovulating women given 150 mcg d-norgestrel (as the dl-racemate) plus 30 mcg ethinyl estradiol over a continuous period of three months indicated no clinically or statistically significant elevation or depression of hormone levels during the course of active drug ingestion, nor in the first post-treatment cycle.

Pharmacokinetics

A human study of the metabolism of ^{14}C-labelled norgestrel, revealed that most of the urinary excretion of norgestrel occurred on the first day. There was no difference in the rate of excretion of norgestrel whether administered orally or intravenously. The amount of radioactivity in plasma fell rapidly within the first few hours and at the end of two days only small amounts were present. The foregoing and other studies with ^{14}C-labelled and unlabelled norgestrel have shown that saturation of the 4,5-double bond with and without concomitant reduction of the 3-carbonyl to a 3-hydroxyl group are important reactions during metabolism.

Special Populations and Conditions

Geriatrics (> 65 years of age)

OVIMA is not indicated for use in postmenopausal women.

Pediatrics

Safety and efficacy of levonorgestrel and ethinyl estradiol tablets have been established in women of reproductive age. Use of this product before menarche is not indicated.

STORAGE AND STABILITY

Store at controlled room temperature 15°C to 30°C. Keep out of reach of children and pets.

OVIMA 21 and OVIMA 28 tablets should be protected from light once opened using the protective covering provided.

Medications should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medications no longer required. These measures will help to protect the environment.

SPECIAL HANDLING INSTRUCTIONS

None

DOSAGE FORMS, COMPOSITION AND PACKAGING

OVIMA tablets are available in 21-day regimen (OVIMA 21) and 28-day regimen (OVIMA 28) blister packages.

Each package consists of 21 round white OVIMA tablets, each tablet containing 150 mcg of levonorgestrel and 30 mcg ethinyl estradiol. In the 28-day regimen package, there are, in addition, 7 round pink tablets containing inert ingredients.

All white, round, flat-faced beveled-edge tablets are engraved with “150” on one side and “30” on the other side. The pink placebo tablets are plain on both sides.

Non Medicinal Ingredients: Each OVIMA tablet contains corn starch, crospovidone, lactose monohydrate, magnesium stearate and povidone.

The inert tablets in the 28-day regimen contain corn starch, crospovidone, FD & C Red no. 3 lake, lactose anhydrous, magnesium stearate and povidone.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

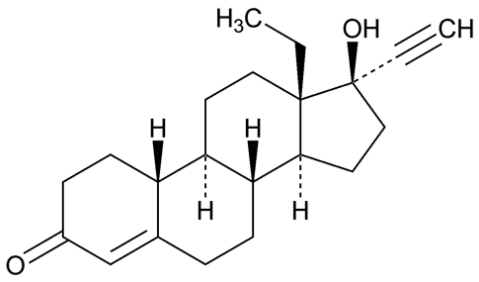
Proper name: Levonorgestrel
Ethinyl Estradiol

Chemical names:

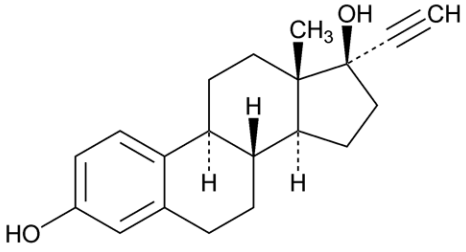
Levonorgestrel: (17a)-(-)-13-ethyl-17-hydroxy-18,19-dinorpregn-4-en-20-yn-3-one

Ethinyl Estradiol: 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol,(17α)-

Structural formulae: Levonorgestrel



Ethinyl Estradiol:



Molecular formula and molecular mass:

Levonorgestrel: $C_{21}H_{28}O_2$

Ethinyl Estradiol: $C_{20}H_{24}O_2$

Molecular Weights:

Levonorgestrel: 312.5 g/mol

Ethinyl Estradiol: 296.41 g/mol

Physicochemical properties:

Solubility:	Levonorgestrel:	Slightly soluble in alcohol, (USP Classification) practically insoluble in water.
	Ethinyl Estradiol:	Insoluble in water, soluble in alcohol, chloroform, ether, in vegetable oils and in solutions of fixed alkali hydroxides.
Melting Point:	Levonorgestrel:	232°C to 239°C
	Ethinyl Estradiol:	180°C to 186°C
Biological Properties:	Levonorgestrel:	A unique, totally synthetic progestogen. Levonorgestrel is the International Nonproprietary Name for this biologically active d-enantiomer of norgestrel.
	Ethinyl Estradiol:	A semi-synthetic estrogen. The presence of the ethinyl group at C 17 on ring D of the steroid nucleus prevents enzymatic degradation of the estradiol molecule and results in an orally active compound.

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on healthy female volunteers. The rate and extent of absorption of levonorgestrel and ethinyl estradiol were measured and compared following a single oral dose (2 x 0.15 mg/0.03 mg tablet) of ^{Pr}Min-Ovral® 21 (levonorgestrel and ethinyl estradiol) and OVIMA in 18 volunteers. The results from measured data are summarized in the following table:

Summary Table of the Comparative Bioavailability Data

Summary Table of the Comparative Bioavailability Data Levonorgestrel (A single 0.30 mg dose: 2 x 0.15 mg) From Measured Data/Fasting Conditions Geometric Mean Arithmetic Mean (CV%)				
Parameter	OVIMA (Apotex Inc.) (Canada)	[Pr]MIN-OVRAL® 21 † (Wyeth Canada) (Canada)	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC_{72} (ng*hr/ mL)	85.268 88.986(30.309)	85.410 87.152(29.497)	99.83%	(90.25%; 110.43%)
AUC_I (ng*hr/ mL)	144.609 175.536 (80.529)	124.911 127.745 (27.582)	115.77%	(95.53%; 140.30%)
C_{max} (ng/ mL)	5.535 5.798 (28.301)	4.837 5.042 (31.438)	114.43%	(105.56%; 124.04%)
T_{max} § (hr)	1.500 (0.667-6.000)	3.000 (1.250 -11.000)		
$T_{½}$ € (hr)	76.223 (96.004)	46.287 (34.164)		
§ Expressed as the median (range). € Expressed as the arithmetic mean (CV %). † [Pr]MIN-OVRAL® 21 is manufactured by Wyeth Canada and was purchased in Canada.				

Summary Table of the Comparative Bioavailability Data

Summary Table of the Comparative Bioavailability Data Ethinyl Estradiol (A single 0.06 mg dose: 2 x 0.03 mg) From Measured Data/Fasting Conditions Geometric Mean# Arithmetic Mean (CV%)				
Parameter	OVIMA (Apotex Inc.) (Canada)	[Pr]MIN-OVRAL® 21 † (Wyeth Canada) (Canada)	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC_t (pg*hr/ mL)	1765.775 1830.200 (29.491)	1876.120 1956.100 (31.685)	94.12%	(89.75%; 98.70%)
AUC_I (pg*hr/ mL)	1875.770 1958.489 (31.854)	1992.229 2097.744 (34.301)	94.15%	(89.55%; 99.00%)
C_{max} (pg/ mL)	136.492 142.335 (35.589)	146.765 151.452 (30.738)	93.00%	(86.19%; 100.35%)

Summary Table of the Comparative Bioavailability Data Ethinyl Estradiol (A single 0.06 mg dose: 2 x 0.03 mg) From Measured Data/Fasting Conditions Geometric Mean[#] Arithmetic Mean (CV%)				
Parameter	OVIMA (Apotex Inc.) (Canada)	[Pr]MIN-OVRAL® 21 [†] (Wyeth Canada) (Canada)	Ratio of Geometric Means (%)	90% Confidence Interval (%)
T_{max}[§] (hr)	1.750 (1.000-4.000)	1.875 (1.000- 2.500)		
$T_{½}$[€] (hr)	18.534 (26.455)	18.382 (26.305)		
[§] Expressed as the median (range). [€] Expressed as the arithmetic mean (CV %). [†] [Pr]MIN-OVRAL® 21 is manufactured by Wyeth Canada and was purchased in Canada.				

The contraceptive efficacy and safety of 150 mcg of levonorgestrel and 30 mcg of ethinyl estradiol has been evaluated in a multi-centre study conducted by 17 investigators.

A highly detailed system of data collection was used in which the subject kept daily records of her tablet-taking, bleeding patterns and side effects, and visited her doctor every three months for regular assessment. This helped to assure that all events during the study were reported accurately and completely and not lost to recall. Women without contraindications were entered into the study at random and not on a selective basis which would bias the results.

A total of 1,084 subjects, 61.5% of proven fertility, completed 8,186 cycles over 23 months of use with levonorgestrel and ethinyl estradiol tablets: 624 completed 6 cycles, 283 completed 12 cycles, 68 completed 18 cycles and 6 completed 23 cycles.

One pregnancy regarded as method failure occurred in the eighth cycle. Two other pregnancies occurred during the third and thirteenth cycles of therapy respectively and were associated with omission of tablets. The overall pregnancy rate calculated by the Life Table Method is 0.88 and the Pearl Index is 0.48 per 100 woman-years. The corrected pregnancy rate (excluding pregnancies which were classified as patient failures) is 0.22 as calculated by the Life Table Method and the Pearl Index is 0.16 per 100 woman-years. This rate was registered in spite of many cycles in which tablets were reportedly missed, in some instances more than 6 tablets in one cycle.

In keeping with the pattern generally noted with combination oral contraceptives, levonorgestrel and ethinyl estradiol tablets maintained a regular cyclic pattern to menstruation. Cycle control as evidenced by cycle length, latent period, and menses length was excellent. The mean length of the menstrual cycle was 28.4 (S.D. 4.8) days, the mean duration of the menstrual flow 4.3 (S.D. 1.2) days. The latent period between the taking of the last pill in a cycle and the onset of the period averaged 2.1 (S.D. 1.3) days in 87.5% (of cycles).

The incidence of missed withdrawal bleeding (termed amenorrhea pretreatment) is low with the

use of levonorgestrel and ethinyl estradiol tablets; 1.5% of total cycles. If one period is missed however, appropriate diagnostic procedures should be undertaken to rule out pregnancy and medication should be discontinued during this time and an alternate method of contraception employed. Prompt return to fertility has been demonstrated following discontinuation of therapy with levonorgestrel and ethinyl estradiol tablets. Of the subjects reporting, 98.7% resumed menses within 30 days of stopping the medication, while five (1.3%) subjects resumed within 60 days.

Plasma progesterone determinations were conducted while on levonorgestrel and ethinyl estradiol tablets, 64 determinations were performed with 60 anovulatory values and 4 ovulatory values. All four ovulatory values were not considered drug-related.

Levonorgestrel and ethinyl estradiol tablets was assessed overall as safe, effective and well-tolerated for a majority of women when taken as directed.

General Information

The following table gives reported pregnancy rates for various forms of birth control, including no birth control. The reported rates represent the number of women out of 100 who would become pregnant in one year.

Table 6: Reported Pregnancies per 100 Women per Year

Combination pill	less than 1 to 2
Intrauterine device (IUD)	less than 1 to 6
Condom with spermicidal foam or gel	1 to 6
Mini-pill	3 to 6
Condom	2 to 12
Diaphragm with spermicidal foam or gel	3 to 18
Spermicide	3 to 21
Sponge with spermicide	3 to 28
Cervical cap with spermicide	5 to 18
Periodic abstinence (rhythm), all types	2 to 20
No birth control	60 to 85

DETAILED PHARMACOLOGY

Animal Pharmacology

Norgestrel is a racemate, composed of equal parts of d- and l-enantiomers. The l-enantiomer has been tested in a broad range of biological assays and its inactivity has been confirmed. The d-enantiomer (named levonorgestrel) accounts for all the biological activity found in norgestrel, as levonorgestrel was twice as potent as the racemate in experiments in which norgestrel was effective.

Intensive biological investigations have been carried out with norgestrel alone and in combination with ethinyl estradiol in rats, mice, rabbits, dogs and monkeys.

In tests for progestational alteration of the endometrium of rabbits, norgestrel by the subcutaneous route proved to be about nine times more active than progesterone and about one hundred times more active than norethisterone by oral and subcutaneous routes. In contrast to norethisterone, which is inactive, norgestrel will maintain pregnancy in spayed laboratory rats and produce endometrial gland development in rabbits when administered directly into the uterine lumen. In a broad series of biological tests, its activities are similar to those of progesterone. Although certain androgenic effects typical of many relatives of 19-nortestosterone are evident at high doses, norgestrel is devoid of such effects at usual clinical doses, and the separation of progestational from androgenic effects for norgestrel is greater than for related compounds. Norgestrel is not estrogenic, nor is it apparently converted *in vivo* to estrogen; it is an exceedingly potent estrogen antagonist. When combined with ethinyl estradiol, norgestrel tends to ameliorate the effects of the estrogen, while the estrogen will modify the effects of the progestogen. In rats, suppression of fertility with norgestrel/ethinyl estradiol combinations is followed by recovery of normal fertility and fecundity.

Additional experiments in laboratory animals were directed toward evaluating the endocrine effects and safety of the norgestrel and ethinyl estradiol formulation at dose levels approximating those employed clinically (on a milligram per kilogram basis). Metrotropic effects (uterine glandular development and growth) were most clearly demonstrated. Blockade of pituitary gonadotrophins can be produced by the estrogenic component alone at the clinical dose range; this pituitary effect does not appear to be modified by addition of the progestogen.

The following properties, observed with high doses of norgestrel or norgestrel/ethinyl estradiol combinations, were absent at doses approximating the clinical range: pregnancy maintenance in spayed female rats; parturition delay in pregnant rats; estrogenic changes in mouse vaginal cytology; anti-estrogenic effect in mouse uterine growth or vaginal smear tests; androgenic, myotrophic or fetal masculinizing effects in rats; claudogenic (antinidatory) effects in rats; thymolymphatic involution in mice; mineralocorticoid effects in rats and dogs and antimineralocorticoid effects in rats. No glucocorticoid (rat liver glycogen) or anti-inflammatory (Selye pouch, TBR-arthritis or granuloma pellet tests) effects have been seen at any dose.

Human Pharmacology

Progestogens can have, in addition to progestational activity, estrogenic, anti-estrogenic and androgenic activity. When combined with estrogen, the progestogen will markedly affect the overall biological activity by producing a synergistic, summative or diminutional effect on activity. Comparisons of progestogen potency are not considered scientifically valid because the effects of one progestogen cannot be directly compared with those of another.[28]

A study of serum luteinizing hormone (LH), follicle stimulating hormone (FSH), progesterone and 17β -estradiol in patients taking 150 mcg d-norgestrel (as the dl-racemate) plus 30 mcg ethinyl estradiol indicated reduction or abolition of the mid-cycle ovulatory peak and post-ovulatory levels commonly associated with these hormones and gonadotrophins respectively. (For plasma progesterone determinations while on levonorgestrel and ethinyl estradiol tablets, see CLINICAL TRIALS).

Endometrial biopsies taken during the course of therapy with 250 mcg d-norgestrel (as the dl-racemate) plus 50 mcg ethinyl estradiol revealed a histological sequence in the menstrual cycle

of early glandular epithelial stimulation followed by later inhibition after the first half of the menstrual cycle. (For endometrial biopsy results with levonorgestrel and ethinyl estradiol tablets, see CLINICAL TRIALS).

Cervical mucus studies with 250 mcg d-norgestrel (as the dl-racemate) plus 50 mcg ethinyl estradiol, and 37.5 mcg d-norgestrel (as the dl-racemate) revealed absence of ferning and decreased spinnbarkeit, indicative of poor conditions for sperm penetration and migration.

The results of assays for prolactin in a group of 11 normally ovulating women given 150 mcg d-norgestrel (as the dl-racemate) plus 30 mcg ethinyl estradiol over a continuous period of three months indicated no clinically or statistically significant elevation or depression of hormone levels during the course of active drug ingestion, nor in the first post-treatment cycle.

A human study of the metabolism of ^{14}C-labelled norgestrel, revealed that most of the urinary excretion of norgestrel occurred on the first day. There was no difference in the rate of excretion of norgestrel whether administered orally or intravenously. The amount of radioactivity in plasma fell rapidly within the first few hours and at the end of two days only small amounts were present. The foregoing and other studies with ^{14}C-labelled and unlabelled norgestrel have shown that saturation of the 4,5-double bond with and without concomitant reduction of the 3-carbonyl to a 3-hydroxyl group are important reactions during metabolism.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

Acute Toxicity

Acute oral toxicity studies have been carried out with oral, intraperitoneal and subcutaneous doses of levonorgestrel alone, ethinyl estradiol alone and in a combination of 5:1 ratio respectively. The following table represents the findings of these studies:

Table 7: - ACUTE TOXICITY

SPECIES	ROUTE OF ADMIN	LEVONORGESTREL	ETHINYL	LD_{50} ETHINYL ESTRADIOL	LEVONORGESTREL + ETHINYL ESTRADIOL (5+1)
Mice	oral	> 4.0 g/kg		> 2.5 g/kg	> 2.5 g/kg
Mice	i.p.	> 3.9 g/kg		0.69 g/kg	1.32-1.65 g/kg
Mice	s.c.	> 4.0 g/kg		> 2.6 g/kg	> 2.5 g/kg
Rats	oral	> 4.0 g/kg		susp. > 5.0 g/kg solu. 1.5g/kg	> 2 g/kg
Rats	i.p.	> 5.0 g/kg		0.97 g/kg	approx. 2 g/kg
Rats	s.c.	> 4.0 g/kg hair loss			> 2 g/kg
Dogs	oral			> 1.0 g/kg	

Both compounds were found to be almost non-toxic in the acute toxicity studies.

CHRONIC TOXICITY

See TOXICOLOGY: Chronic Toxicity: Table 8.

Table 8 - CHRONIC TOXICITY

SPECIES	DRUGS DOSE AND ROUTE OF ADMINISTRATION	DURATION OF ADMINISTRATION	SYMPTOMS	HISTOPATHOLOGY
RAT 16/sex/group	Norgestrel Oral – mg/kg 0.0001%, 0.0005%, 0.0025%	26 weeks	No signs and symptoms of toxicity.	No histopathological changes.
	Levonorgestrel Oral – mg/kg 0.00005%, 0.00025%, 0.00125%	26 weeks	Significant less weight gain in low dose females, no other signs of toxicity.	No abnormal histopathology.
DOG 6/sex/group	Levonorgestrel Oral - mg/kg 0.05, 0.1, 0.5	26 weeks	No estrus in any dog, mammary enlargement in all but 2 females and 8 males. Dose related clitoral reddening and enlargement. Significant decrease in cholesterol in all dosage groups.	No drug related effects on ophthalmology, ECG, hemostatic functions, urinalysis or organ weight.
DOG 16 females/dose	Norgestrel Oral - mg/kg 0.0, 0.003, 0.015,0.0375	continuous 7 years	Estrus inhibited in all but low dosage group. Uterine enlargement and endometrial hyperplasia at 0.015 and 0.0375 mg/kg.	Norgestrel 0.0375 mg group - many dogs with cysts and absence of luteal phase. 1 dog mammary carcinoma (0.0375)
	Levonorgestrel Oral - mg/kg 0.5	cyclic - 7 years	Enlarged clitoris on majority of dogs. Hematocrit and hemoglobin low or SGPT Increased significantly. Fibrinogen increased.	Increase in benign mammary adenomas. 1 dog adenocarcinoma. Many vaginal cysts and absence of luteal phase.
DOG 16 females/dose	Levonorgestrel Oral - mg/kg 0.01, 0.05, 0.125	cyclic - 7 years	No unexpected findings. The only drug effects observed were at the higher dose levels, were endocrine related and were considered to be related to the desired pharmacological effects of a progestational agent.	No apparent drug-related changes during the postmortem examination.

Table 8 - CHRONIC TOXICITY

SPECIES	DRUGS DOSE AND ROUTE OF ADMINISTRATION	DURATION OF ADMINISTRATION	SYMPTOMS	HISTOPATHOLOGY
RHESUS MONKEY 16 females/dose	Norgestrel Oral- mg/kg 0.0, 0.003, 0.015, 0.075	Continuous 10 years (120 months)	Red vaginal discharge less frequent in 0.015 and 0.075 mg/kg group.	Mammary nodules in 3 animals at 0.075 mg/kg. 1 animal at 0.003 and 0.015 mg/kg.
	Levonorgestrel Oral - mg/kg 1.0	cyclic - (21 days) 10 years (120 months)	Red vaginal discharge more frequent in withdrawal period. Fibrinogen levels increased.	Mammary nodule in 1 animal.
MICE 40/sex/dose	I Norgestrel II Ethinyl Estradiol III Norgestrel + Ethinyl Estradiol (10+1) Oral - mg/kg 0.02 + 0.002 0.7 + 0.07 2.0 + 0.2 3.0 + 0.3	80 weeks	Ethinyl Estradiol depressed weight gain in 3 highest dosage groups. Norgestrel + Ethinyl Estradiol-depressed weight gain in 3 highest dosage groups. Norgestrel-no effects.	Ethinyl Estradiol-significant increase in malignant tumours. Lymphocarcinoma-males interstitial tumours-females. Ethinyl Estradiol + Norgestrel-same. Norgestrel-no significant tumorigenic effect.
RAT 40/sex/dose	I Norgestrel II Ethinyl Estradiol III Norgestrel + Ethinyl Estradiol (10+1) Oral - mg/kg 0.02 + 0.002 0.5 + 0.05 2.0 + 0.2	104 weeks	Norgestrel-no effects. Ethinyl Estradiol-dosage related decrease in body weight gain. Norgestrel + Ethinyl Estradiol-dosage related decrease in body weight gain.	Malignant and benign mammary tumours were significantly increased over controls in both male and females at the two highest dosage levels of Ethinyl Estradiol either alone or in combination with Norgestrel. Hematological changes included are one case of Leukemia in low

Table 8 - CHRONIC TOXICITY

SPECIES	DRUGS DOSE AND ROUTE OF ADMINISTRATION	DURATION OF ADMINISTRATION	SYMPTOMS	HISTOPATHOLOGY
DOG 12 females/dose	I Norgestrel II Ethinyl Estradiol III Norgestrel + Ethinyl Estradiol Oral - mg/kg I 0.1-0.25 II 0.01 III 0.1 + 0.025 0.1 + 0.01 0.25 + 0.025	7 years	Norgestrel-increase in body weight at 0.1 mg/kg. Slight to moderate increase SGPT values in treated groups also increase in fibrinogen in some animals. Norgestrel alone or in combination with Ethinyl Estradiol also suppressed estrus.	Dose related increase in mammary adenomas in the Norgestrel treated groups. Possible indication of an increase in benign adenomas and intraductal papillomas after high doses of Norgestrel.
RHESUS MONKEY 16 females/dose	I Norgestrel II Ethinyl Estradiol III Norgestrel + Ethinyl Estradiol Oral - mg/kg 1 0.02, 0.1, 0.5 II 0.002, 0.01, 0.05 III 0.02 + 0.002 0.1 + 0.01 0.5 + 0.05	10 years	Increase in body weight gain in the Norgestrel 0.5 mg/kg group. Fibrinogen levels increased in monkeys receiving Norgestrel alone or in combination with Ethinyl Estradiol. A higher rate with retinal depigmentation in the groups treated with Ethinyl Estradiol alone or in combination with Norgestrel.	No abnormal findings.

Reproduction and Teratology

At doses in the clinical range, norgestrel, ethinyl estradiol and their combinations have no demonstrable effects on pregnant rats, their pregnancies, their offspring or the reproductive potential of the young.

Also at doses approximating the clinical range, norgestrel and/or ethinyl estradiol have no observable effects on lactating rats, the lactation process or the nursing young.

At doses in the clinical range and above, a small dose-related increase in the number of abnormal fetuses is observed in mice treated during pregnancy with norgestrel/ethinyl estradiol combinations in a ratio of 5:1. Abnormalities include open eye, cleft palate, exencephaly and umbilical hernia. Rabbits treated during pregnancy with doses of norgestrel and ethinyl estradiol in the clinical range and above, failed to demonstrate any teratogenic potential for the drug.

REFERENCES

1. Allen HH. Clinical assessment of a low dose estrogen low dose progestogen combined oral contraceptive. Curr Med Res Opin.1974; 2:101-108.
2. Binkley KE, Davis A, 3rd. Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema. J Allergy Clin Immunol 2000; 106(3);546-50. estrogen-dependent inherited form of angioedema. J Allergy Clin Immunol 2000; 106(3);546-50.
3. Bork K, Fischer B, Dewald G. Recurrent episodes of skin angioedema and severe attacks of abdominal pain induced by oral contraceptives or hormone replacement therapy. AmJ Med 2003;114(4);294-8.
4. Boyo EJ, Theis MK, Vaughan TL, Nicol-Blades B. Increased risk of inflammatory bowel disease associated with oral contraceptive use. Am J Epidemiol 1994; 140(3):268 - 78.
5. Dionne P, Vickerson F. A double-blind comparison of two oral contraceptives containing 50 mcg and 30 mcg ethinyl estradiol. Curr Ther Res. 1974; 16:281-288.
6. Drugs taken with oral contraceptives. Br Med J. 1967; 1:287.
7. Fotherby K. A metabolic assessment of different oral contraceptives. J Obstet Gynecol. 1983; 3, Suppl. 2:S77-S82.
8. Fotherby K. Oral contraceptives, lipids and cardiovascular disease. Contraception. 1985; 31(4):367-394.
9. Francis WG, Dalziel D. Accidental ingestion of oral contraceptives by children. Can Med Assoc J. 1965; 92:191.
10. Godet PG, May GR, Sutherland LR. Meta-analysis of the role of oral contraceptive agents in inflammatory bowel disease. Gut 1995; 37(5):668-73.
11. Godsland IF, Crook D, Simpson R, Proudler T, Felton C, Lees B, Anyaoku V, Devenport M,

WynnV. The effects of different formulations of oral contraceptive agents on lipid and carbohydrate metabolism. N EngI J Med. 1990; 323:1375-1381.

12. Goldzieher JW. Advances in oral contraception. An international review of levonorgestrel and ethinyl estradiol. J Reprod Med. 1983; 28(1), Suppl.:53-56.
13. Greenblatt RB. An interpretation of oral contraceptive epidemiologic studies. In: Brosens I, ed. New considerations in oral contraception. New York: Biomedical Information Corporation Publications, 1982: 3-20.
14. Guillebaud J. The 150/30 formulation: experience in the United Kingdom. J Reprod Med. 1983; 28(1):66-70.
15. Haspels AA. Clinical experience with a low-dose contraceptive agent: European studies. J Reprod Med. 1983; 28(1):71-76.
16. Heikkila K, Haukkamaa M, Luukkainen T. Levonorgestrel in mild and plasma of breast-feeding women with a levonorgestrel-releasing IUD. Contraception. 1982; 25(1):41-49.
17. Hull VJ: The effects of hormonal contraceptives on lactation: Current findings, methodological considerations, and future priorities. Stud Fam Plann 12(4): 134-155, 1981.
18. Jones RC, Singer AC, Edgren RA. The biological activities of norgestrel and its enantiomers. lnt J Fertil. 1979; 24(1):39-43.
19. Jones RC, Corbin A. Preclinical endocrinology of levonorgestrel, an orally active progestational agent. (Data on file). Wyeth-Ayerst Canada Inc., North York, Ontario, Canada. 1981.
20. Koetsawang S: The effects of contraceptive methods on the quality and quantity of breast milk. Int J Gynecol Obstet 25(Suppl) 1987: 115-127.
21. Logan RF, Kay CR. Oral contraception, smoking and inflammatory bowel disease-findings in the Royal College of General Practitioners Oral Contraception Study. Int J Epidemiol 1989;18(1):105-7.
22. Lonnerdal B et al: Effect of oral contraceptives on composition and volume of breast milk. Am J Clin Nutrit 1980; 33: 816-824.
23. Moggia AV. Contraception with levonorgestrel, 0.15 mg, and ethinyl estradiol, 0.03 mg: clinical studies in Latin America. J Reprod Med. 1983; 28(1):77-80.
24. Multi-centre clinical trial (levonorgestrel 0.15 mg + ethinyl estradiol 0.03 mg). U.S.A. (Data on file). Wyeth-Ayerst Canada Inc., North York, Ontario, Canada.
25. Nilsson S et al: Ethinyl estradiol in human milk and plasma after oral administration. Contraception 1978; 17(2): 131-139.
26. Nilsson S et al: d-Norgestrel concentrations in maternal plasma, milk and child plasma during administration of oral contraceptives to nursing women. Am J Obstet Gynecol 1977; 129(2): 178-184.

27. Nzeako UC, Frigas E, Tremaine WJ. Hereditary angiodema; a broad review for clinicians. Arch Intern Med 2001;161(20):2417-29.

28. Oral Contraceptives, 1994. A report by the Special Advisory Committee On Reproductive Physiology. To the Drugs Directorate, Health Protection Branch, Health and Welfare, Canada.

29. Ramcharan S, Pellegrin FA, Ray R, Hsu J-P, Vessey MP. General summary of findings; general conclusions; implications, In:The Walnut Creek Contraceptive Drug Study; a prospective study of the side effects of oral contraceptives. Volume III: An interim report; a comparison of disease occurrence leading to hospitalization or dealth in users and nonusers of oral contraceptives. NIH Publication No. 81-564. Bethesda (MD): US Department of Health, Education, and Welfare, Centre for Population Research; 1981. p. 211-38.

30. Realini JP, Goldzieher JW. Oral contraceptives and cardiovascular disease: a critique of the epidemiologic studies. Am J Obstet Gynecol. 1985; 152(6):729-798.

31. Rozenbaum H. Relationships between chemical structure and biological properties of progestogens. Am J Obstet Gynecol. 1982; 142(6), Part 2:719-724.

32. Sondheimer S. Metabolic effects of the birth control pill. Clin Obstet Gynecol. 1981; 24(3):927-941.

33. Sturtevant FM. Breast cancer and oral contraceptives. (Correspondence). Lancet. November 12, 1983; 1145.

34. Sturtevant FM. Breast cancer and oral contraceptives: critique of the proposition that high potency progestogen products confer excess risk. Biomed Pharmacother. 1984; 38:371-379.

35. Sutherland LR, Ramcharan S, Bryant H, Fick G. Effect of oral contraceptive use on reoperation following surgery for Crohn's disease. Dig Dis Sci 1992; 37(9);1377-82.

36. The Centres for Disease Control, Cancer and Steroid Hormone Study. Long-term oral contraceptive use and the risk of breast cancer. JAMA. 1983; 249:1591-1595.

37. Toddywalla VS et al: Release of 19-nor-testosterone type of contraceptive steroids through different drug delivery systems into serum and breast milk of lactating women. Contraception 1980; 21(3): 217-223.

38. Toxicity of oral contraceptives. Br Med J. 1967; 1:38.

39. Vessey M, Jewell D, Smith A, Yeates D, McPherson K. Chronic inflammatory bowel disease, cigarette smoking, and use of oral contraceptives; findings in a large cohort study of women of childbearing age. Br Med J (Clin Res Ed) 1986; 292 (6528);1101-3.

40. WHO. Medical eligibility criteria for contraceptive use. Geneva:World Health Organization, Reproductive Health and research; 2004:1-176.

41. Woutersz TB. A new low estrogen, low progestogen combined oral contraceptive. Curr Med Res Opin. 1974; 2:95.

42. Product Monograph – Min-Ovral® 21 and Min-Ovral®28 (150 mcg levonorgestrel and 30 mcg ethinyl estradiol). ® T.M. Wyeth LLC and Pfizer Canada ULC., Licensee. Date of

Revision: AUG 25, 2025, Control No: 294279.

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

PrOVIMA® 21 and PrOVIMA®28
Levonorgestrel and Ethinyl Estradiol Tablets

150 mcg levonorgestrel and 30 mcg ethinyl estradiol tablets

This leaflet is part III of a three-part "Product Monograph" published when OVIMA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about OVIMA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- To prevent pregnancy

What it does:

OVIMA is a birth control pill (oral contraceptive) that contains two female sex hormones (levonorgestrel and ethinyl estradiol).

It has been shown to be highly effective in preventing pregnancy when taken as prescribed by your doctor. Pregnancy is always more risky than taking birth control pills except in smokers older than age 35.

Birth control pills work by inhibiting the monthly release of an egg(s) by the ovaries. Some studies have demonstrated changes in the endometrium (lining of the womb) and mucus produced by the cervix (opening of the uterus) with the use of birth control pills.

Effectiveness of Birth Control Pills

Combination birth control pills are more than 99 percent effective in preventing pregnancy when:

- the pill is **TAKEN AS DIRECTED**, and
- the amount of estrogen is 20 micrograms or more.

A 99 percent effectiveness rate means that if 100 women used birth control pills for one year, one woman in the group would get pregnant.

The chance of becoming pregnant increases with incorrect use.

Other Ways to Prevent Pregnancy

Other methods of birth control are available to you. They are usually less effective than birth control pills. When used properly, however, other methods of birth control are effective enough for many women.

The following table gives reported pregnancy rates for various forms of birth control, including no birth control. The reported rates represent the number of women out of 100 who would become pregnant in one year.

Reported Pregnancies per 100 Women per Year:

Combination pill	less than 1 to 2
Intrauterine device (IUD)	less than 1 to 6
Condom with spermicidal foam	1 to 6
or gel	3 to 6
Mini-pill	2 to 12
Condom	3 to 18
Diaphragm with spermicidal	3 to 21
foam or gel	3 to 28
Spermicide	5 to 18
Sponge with spermicide	2 to 20
Cervical cap with spermicide	60 to 85
Periodic abstinence (rhythm), all types	
No birth control	

Pregnancy rates vary widely because people differ in how carefully and regularly they use each method. (This does not apply to IUDs since they are implanted in the uterus). Regular users may achieve pregnancy rates in the lower ranges. Others may expect pregnancy rates more in the middle ranges.

The effective use of birth control methods other than birth control pills and IUDs requires more effort than taking a single pill every day. It is an effort that many couples undertake successfully

When it Should not be Used:

The birth control pill is not suitable for every woman. In a small number of women, serious side effects may occur. Your doctor can advise you if you have any conditions that would pose a risk to you. If you see a different doctor, inform him/her that you are taking birth control pills. Tell the doctor that your birth control pills are OVIMA. The use of the birth control pill should always be supervised by your doctor.
You should not use OVIMA if you have or have had any of the following conditions:

- History of or actual heart attack, chest pain (angina pectoris) or stroke;
- Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), eyes or elsewhere;
- Hereditary or acquired blood clotting disorders;

- Known or suspected cancer of the breast, sex organs, or certain estrogen-dependent cancers;
- Unexplained vaginal bleeding (until a diagnosis is reached by your doctor);
- Partial or complete loss of vision or other vision problems caused by vascular disease (blood vessel disease of the eye);
- History of or actual liver disease or history of or actual benign or malignant liver tumor;
- Jaundice (yellowing of the skin and eyes) or liver disease if still present;
- Heart valve or heart rhythm disorders that may be associated with formation of blood clots;
- Diabetes affecting your circulation;
- Migraines (current or history) with neurological symptoms such as aura (visual or sensory disturbance);
- Uncontrolled high blood pressure;
- Hypersensitivity(allergy) to any of the components of OVIMA (levonorgestrel and ethinyl estradiol tablets) (see *What the important non-medicinal ingredients are)*;
- Known or suspected pregnancy. Birth control pills should never be taken if you think you are pregnant. They will not prevent the pregnancy from continuing. There is no conclusive evidence, however, that the pill can damage a developing child when taken inadvertently during early pregnancy;
- Pancreatitis associated with severe hypertriglyceridemia (current or history). Pancreatitis is the inflammation of the pancreas, marked by abdominal pain, whereas severe hypertriglyceridemia is a very high level of triglycerides in the blood, and may show no symptoms.
- Are using anti-viral medications to treat Hepatitis C Virus (HCV) which contain combination of ombitasvir, paritaprevir, ritonavir and dasabuvir with or without ribavirin.

What the medicinal ingredients are:
Levonorgestrel and Ethinyl Estradiol

What the important non-medicinal ingredients are:

Each OVIMA tablet contains corn starch, crospovidone, lactose monohydrate, magnesium stearate and povidone.

The inert tablets in the 28-day regimen contain corn starch, crospovidone, FD&C Red no. 3 lake, lactose anhydrous, magnesium stearate and povidone.

What dosage forms it comes in:

OVIMA (levonorgestrel and ethinyl estradiol tablets) are available in a 21-day regimen (OVIMA 21) and a 28-day regimen (OVIMA 28)

OVIMA 21: Each package contains 21 white tablets. Each white tablet contains 150 mcg levonorgestrel and 30 mcg ethinyl estradiol.

OVIMA 28: Each blister pack contains 21 white and 7 pink, tablets. Each white tablet contains 150 mcg levonorgestrel and 30 mcg ethinyl estradiol. The pink tablets are inactive (do not contain hormones).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in birth control pill users over 35 years of age. Women who use birth control pills should not smoke.

Birth control pills DO NOT PROTECT against sexually transmitted infections (STIs), including HIV/AIDS.

For protection against STIs, it is advisable to use latex or polyurethane condoms IN COMBINATION WITH birth control pills.

There are conditions that your doctor will want to watch closely or that might cause your doctor to recommend a method of contraception other than birth control pills.

BEFORE you use OVIMA talk to your doctor or pharmacist if the following apply to you:

- Breast conditions
  - A strong family history of breast cancer
  - Breast disorders including pain, discharge from the nipples, thickenings, or lumps. In some circumstances, benefit may be derived from taking the pill; in other cases, adverse effects may follow.
- Diabetes
- High blood pressure
- Abnormal levels of fats in the bloodstream (high cholesterol or triglycerides)
- Cigarette Smoking
- Heart or kidney disease
- Epilepsy/seizures
- History of Depression

- Fibroid tumours of the uterus
- Gallbladder or pancreatic disease
- History of liver disease or jaundice
- Family history of blood clots, heart attacks or strokes.
- May be pregnant or breast feeding
- Have systemic lupus erythmatosus
- Have inflammatory bowel disease such as Crohn's disease or ulcerative colitis
- Have haemolytic uremic syndrome
- Have sickle cell disease
- Have problems with the valves in your heart and/or have irregular heart rhythm
- Wear contact lenses
- Obesity
- Have Hepatitis C

If you see a different doctor, inform him or her that you are using OVIMA.

Tell your doctor if you are scheduled for any laboratory tests since certain blood tests may be affected by hormonal contraceptives.

Also tell your doctor if you are scheduled for **MAJOR** surgery, recent delivery, or second-trimester abortion. You should consult your doctor about stopping the use of OVIMA four weeks before major surgery and not using OVIMA for a time period after surgery or during prolonged bed rest.

OVIMA should be used only under the supervision of a doctor, with regular follow-up to identify side effects associated with its use. Your visits may include a blood pressure check, a breast exam, an abdominal exam and a pelvic exam, including a Pap smear. Visit your doctor three months or sooner after the initial examination. Afterward, visit your doctor at least once a year.

Use OVIMA only on the advice of your doctor and carefully follow all directions given to you. You must use the birth control pill exactly as prescribed. Otherwise, you may become pregnant. If you and your doctor decide that, for you, the benefits of OVIMA outweigh the risks, you should be aware of the following:

THE RISKS OF USING BIRTH CONTROL PILLS

1. **Circulatory disorders (including blood clot in legs, lungs, heart, eyes or brain)**

   Women who use hormonal contraceptives have a higher incidence of blood clots. Blood clots are the most common serious side effects of birth control pills. The risk of developing clots is especially high during the first year a woman ever uses a hormonal contraceptive. Clots can occur in many areas of the body.

   Be alert for the following symptoms and signs of serious adverse effects. Call your doctor immediately if they occur:

   - Sharp pain in the chest, coughing blood, or sudden shortness of breath. These symptoms could indicate a possible blood clot in the lung;
   - Pain and/or swelling in the calf. These symptoms could indicate a possible clot in the leg;
   - Crushing chest pain or heaviness. These symptoms could indicate a possible heart attack;
   - Sudden severe or worsening headache or vomiting dizziness or fainting, disturbances of vision or speech, or weakness or numbness in an arm or leg. These symptoms could indicate a possible stroke;
   - Sudden partial or complete loss of vision. This symptom could indicate a blood clot in the eye.

   Any of these conditions can cause death or disability. Clots also occur rarely in the blood vessels of the eye, resulting in blindness or impaired vision or in a blood vessel leading to an arm or leg, resulting in damage to or loss of a limb.

   The risk of clotting seems to increase with higher estrogen doses. **It is important, therefore, to use as low a dosage of estrogen as possible.**

2. **Breast cancer**
   The most significant risk factors for breast cancer are increasing age and a strong history of breast cancer in the family (mother or sister). Other established risk factors include obesity, never having children, and having your first full-term pregnancy at a late age.

   Some women who use birth control pills may be at increased risk of developing breast cancer before menopause, which occurs around age 50. These women may be long-term users of birth control pills (more than eight years) or women who start using Birth control pills at an early age. In a few women, the use of Birth control pills may

accelerate the growth of an existing but undiagnosed breast cancer. Early diagnosis, however, can reduce the effect of breast cancer on a woman's life expectancy. The potential risks related to birth control pills seem to be small, however; a yearly breast examination by a doctor is recommended for all women.

ASK YOUR DOCTOR FOR ADVICE AND INSTRUCTIONS ON REGULAR SELF-EXAMINATION OF YOUR BREASTS.

3. **Cervical cancer**

Some studies have found an increase of cancer of the cervix in women who use hormonal contraceptives, although this finding may be related to factors other than the use of oral contraceptives. However, there is insufficient evidence to rule out the possibility that oral contraceptives may cause such cancers.

Chronic infection with the Human Papilloma Virus (HPV) is believed to be the most important risk factor for cervical cancer. In women who use COCs for a long time the chance of getting cervical cancer may be slightly higher. This finding may not be caused by the Pill itself but may be related to sexual behavior and other factors.

4. **Liver tumors**

The short and long-term use of birth control pills have also been linked with the growth of liver tumors or liver injury (e.g., hepatitis, hepatic function abnormal). Such tumors are extremely rare. Contact your doctor immediately if you experience severe pain or a lump in the abdomen.

5. **Gallbladder disease**

Users of birth control pills have a greater risk of developing gallbladder disease requiring surgery within the first year of use. The risk may double after four or five years of use.

6. **Use in pregnancy**

Birth control pills should not be taken by pregnant women. They will not prevent the pregnancy from continuing. There is no evidence, however, that the birth control pill can damage a developing child. You should check with your doctor about risks to your unborn child from any medication taken during pregnancy.

7. **Use after pregnancy, miscarriage or an abortion**

Your doctor will advise you of the appropriate time to start the use of OVIMA after childbirth, miscarriage, or therapeutic abortion.

8. **Pregnancy after stopping OVIMA**

You will have a menstrual period when you stop using OVIMA. You should delay pregnancy until another menstrual period occurs within four to six weeks. In this way the pregnancy can be more accurately dated. Contact your doctor for recommendations on alternate methods of contraception during this time.

9. **Use while breast feeding**

If you are breast-feeding, consult your doctor before starting the birth control pill. The hormones in birth control pills are known to appear in breast milk. Adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. You should use another method of contraception. The use of oral contraceptives is generally not recommended until the nursing mother has completely weaned her child.

INTERACTIONS WITH THIS MEDICATION

Certain drugs may interact with birth-control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. You may also need to use a nonhormonal method of contraception during any cycle in which you take drugs that can make oral contraceptives less effective.

Drugs that may interact with OVIMA include:

- drugs used for epilepsy such as barbiturates (e.g. phenobarbital) and phenytoin, primidone, topiramate, carbamazepine
- certain drugs used in the treatment of tuberculosis (eg. Rifampicin, rifabutin)
- drugs used for HIV or AIDS such as ritonavir
- herbal products containing St. John's Wort (Hypericum perforatum)
- antibiotics (e.g. penicillins, tetracyclines) for infectious diseases
- cyclosporine
- antifungals (griseofulvin)
- cholesterol-lowering drugs (eg. clofibrate)
- antihypertensive drugs (for high blood pressure)
- antidiabetic drugs and insulin (for diabetes)
- prednisone
- sedatives and hypnotics (eg, benzodiazepines, barbiturates, chloral

hydrate, glutethimide, meprobamate)
- antidepressants (e.g. clomipramine)
- other drugs such as phenylbutazone, analgesics, modafinil, troleandomycin, Vitamin E and Vitamin B_{12}.
- anti-viral hepatitis C virus (HCV) medicinal products such as ombitasvir, paritaprevir, ritonavir and dasabuvir, with or without ribavirin.

Please inform your doctor and pharmacist if you are taking or have recently taken any other drugs or herbal products, even those without a prescription. Also tell any other doctor or dentist who prescribes another drug (or the dispensing pharmacist) that you use OVIMA. They can tell you if you need to use an additional method of contraception and if so, for how long.

This is not a complete list of possible drug interactions with OVIMA. Talk to your doctor for more information about drug interactions.

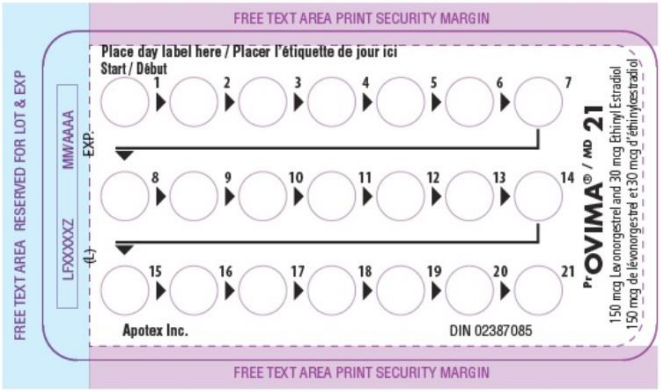
PROPER USE OF THIS MEDICATION

Usual dose:

HOW TO TAKE OVIMA:

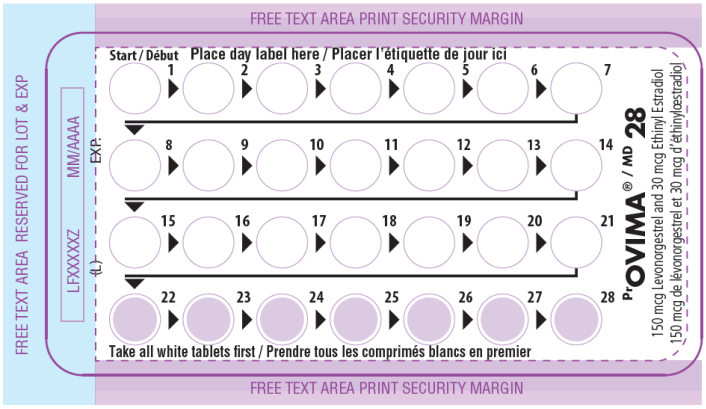
1. **READ THESE DIRECTIONS**
   - Before you start taking your pills, and
   - Any time you are not sure what to do.

2. LOOK AT YOUR PILL PACK to see if it has 21 or 28 pills:
   - 21-Pill Pack: 21 active pills (with hormones) taken daily for three weeks, and then no pills taken for one week;



Or

- 28-Pill Pack: 21 active pills (with hormones) taken daily for three weeks, and then seven "reminder" pills (no hormones) taken daily for one week.



DIRECTIONS FOR USE OF THIS STICKER:

MON/LUN	TUE/MAR	WED/MER	THU/JEU	FRI/VEN	SAT/SAM	SUN/DIM
TUE/MAR	WED/MER	THU/JEU	FRI/VEN	SAT/SAM	SUN/DIM	MON/LUN
WED/MER	THU/JEU	FRI/VEN	SAT/SAM	SUN/DIM	MON/LUN	TUE/MAR
THU/JEU	FRI/VEN	SAT/SAM	SUN/DIM	MON/LUN	TUE/MAR	WED/MER
FRI/VEN	SAT/SAM	SUN/DIM	MON/LUN	TUE/MAR	WED/MER	THU/JEU
SAT/SAM	SUN/DIM	MON/LUN	TUE/MAR	WED/MER	THU/JEU	FRI/VEN
SUN/DIM	MON/LUN	TUE/MAR	WED/MER	THU/JEU	FRI/VEN	SAT/SAM

Peel the sticker off for the day of the week you plan to start your pills. Place the sticker over the space provided for the days of the week and make sure it lines up with the pills. This sticker will help to remind you to take your pill every day.

3. You may wish to use a second method of birth control (e.g. latex condoms and spermicidal foam or gel) for the first seven days of the first cycle of pill use. This will provide a back-up in case pills are forgotten while you are getting used to taking them.

4. **When receiving any medical treatment, be sure to tell your doctor that you are using birth control pills.**

5. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST THREE MONTHS ON THE PILL. If you do feel sick, do not stop taking OVIMA. The problem will usually go away. If it does not go away, check with your doctor or clinic.

6. MISSING PILLS ALSO CAN CAUSE SOME SPOTTING OR LIGHT BLEEDING, even if you make up the missed pills. You also could feel a little sick to your stomach on the days you take

two pills to make up for missed pills.

7. IF YOU MISS PILLS AT ANY TIME, YOU COULD GET PREGNANT. THE GREATEST RISKS FOR PREGNANCY ARE:
   - when you start a pack late or
   - when you miss pills at the beginning or at the very end of the pack.

8. ALWAYS BE SURE YOU HAVE READY:
   - ANOTHER KIND OF BIRTH CONTROL (such as latex condoms and spermicidal foam or gel) to use as a back-up in case you miss pills, and
   - AN EXTRA PACK OF PILLS.

9. IF YOU EXPERIENCE VOMITING OR DIARRHEA, OR IF YOU TAKE CERTAIN MEDICINES, such as antibiotics, your pills may not work as well. Use a back-up method, such as latex condoms and spermicidal foam or gel, until you can check with your doctor or clinic.

10. IF YOU FORGOT MORE THAN ONE PILL TWO MONTHS IN A ROW, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.

11. IF YOUR QUESTIONS ARE NOT ANSWERED HERE, CALL YOUR DOCTOR OR CLINIC.

WHEN TO START THE FIRST PACK OF PILLS

BE SURE TO READ THESE INSTRUCTIONS:
- before you start taking your pills, and
- any time you are not sure what to do.

Decide with your doctor or clinic what is the best day for you to start taking your first pack of pills. Your pills may be either a 21-day or a 28-day type.

A. 21-DAY COMBINATION

With this type of birth control pill, you are on pills for 21 days and off pills for seven days. You must not be off the pills for more than seven days in a row.

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** Your doctor may advise you to start taking the pills on Day 1, on Day 5, or on the first Sunday after your period begins. If your period starts on Sunday, start that same day. If OVIMA tablets administration is initiated after Day 1 of the first menstrual cycle or postpartum, contraceptive reliance should not be placed on OVIMA until after the first seven active tablets have been taken for seven consecutive days. Nonhormonal methods of contraception (such as latex condoms and spermicidal foam or gel) should be used for the first 7 days of tablet taking.

2. Take one pill at approximately the same time every day for 21 days, THEN TAKE NO PILLS FOR SEVEN DAYS. Start a new pack on the eighth day. You will probably have a period during the seven days off the pill. (This bleeding may be lighter and shorter than your usual period).

TWO WAYS TO REMEMBER IN WHAT ORDER TO TAKE THE PILLS

1. Follow the days of the week (as shown above the pills).
2. Always finish the white tablets before going on to the week when you are off pills.

B. 28-DAY COMBINATION

With this type of birth control pill, you take 21 pills that contain hormones and seven pills that contain no hormones.

1. THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE. Your doctor may advise you to start taking the pills on Day 1, on Day 5, or on the first Sunday after your period begins. If your period starts on Sunday, start that same day. If OVIMA tablets administration is initiated after Day 1 of the first menstrual cycle or postpartum, contraceptive reliance should not be placed on OVIMA until after the first seven active tablets have been taken for seven consecutive days. Nonhormonal methods of contraception (such as latex condoms and spermicidal foam or gel) should be used for the first 7 days of tablet taking.

2. Take one pill at approximately the same time every day for 28 days. Begin a new pack the next day, NOT MISSING ANY DAYS. Your period should occur during the last seven days of using that pill pack.

IMPORTANT: PLEASE READ

TWO WAYS TO REMEMBER IN WHAT ORDER TO TAKE THE PILLS

1. Follow the days of the week (as shown above the pills).
2. Always finish the white tablets before going on to the pink numbered pills.

WHAT TO DO DURING THE MONTH

1. TAKE A PILL AT APPROXIMATELY THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.

2. Try to associate taking your pill with some regular activity such as eating a meal or going to bed.
3. Do not skip pills even if you have bleeding between monthly periods or feel sick to your stomach (nausea).
4. Do not skip pills even if you do not have sex very often.

5. WHEN YOU FINISH A PACK
   - 21 PILLS

   WAIT SEVEN DAYS to start the next pack. You will have your period during that week.

   - 28 PILLS

   Start the next pack ON THE NEXT DAY. Take one pill every day. Do not wait any days between packs.

Overdose:

Overdosage may cause nausea, vomiting, breast tenderness, dizziness, abdominal pain, and fatigue/drowsiness. Withdrawal bleeding may occur in females.

If you think you, or a person you are caring for, have taken too much OVIMA 21 and OVIMA 28, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

WHAT TO DO IF YOU MISS PILLS
Birth control pills may not be as effective if you miss pills. The following chart outlines the actions you should take if you miss one or more of your birth control pills. Match the number of pills missed with the appropriate starting time for your type of pill pack.

SUNDAY START	**OTHER THAN SUNDAY START**
Miss One Pill	**Miss One Pill**
Take it as soon as you remember, and take the next pill at the usual time. This means that you might take two pills in one day.	Take it as soon as you remember, and take the next pill at the usual time. This means that you might take two pills in one day.
Miss Two Pills in a Row	**Miss Two Pills in a Row**
First two weeks 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. **Third week** 1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. **If You Miss Two Periods in a Row, Call your Doctor or Clinic.**	**First two weeks** 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. **Third week** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. **If You Miss Two Periods in a Row, Call your Doctor or Clinic.**
Miss Three or More Pills in a Row	**Miss Three or More Pills in a Row**
Anytime in the cycle 1. Keep taking one pill a day until Sunday.	**Anytime in the cycle** 1. Safely dispose of the rest of the pill pack

2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. **If You Miss Two Periods in a Row, Call your Doctor or Clinic.**	and start a new pack that same day. 2. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. **If You Miss Two Periods in a Row, Call your Doctor or Clinic.**

NOTE: 28-DAY PACK – If you forget any of the seven "reminder" pills (without hormones) in Week 4, just safely dispose of the pills you missed. Then keep taking one pill each day until the pack is empty. You do not need to use a back-up method.

Always be sure you have on hand:

- a non-hormonal back-up method of birth control (such as latex condoms and spermicidal foam or gel) in case you miss pills, and
- an extra, full pack of pills.

IF YOU FORGET MORE THAN ONE PILL TWO MONTHS IN A ROW, TALK TO YOUR DOCTOR OR CLINIC about ways to make pill-taking easier or about using another method of birth control.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Some users of birth control pills have unpleasant side effects. Most side effects are temporary and are not hazardous to the health.

There may be tenderness of the breast, nausea, and vomiting. Some users will experience weight gain or loss. Many of these side effects occurred with high-dose combination birth control pills. These side effects are less common with the low-dose pills prescribed today.

Unexpected vaginal bleeding or spotting and changes in the usual menstrual period may also occur. These side effects usually disappear after the first few cycles. They are not an indication to stop taking birth control pills. Unless more significant complications occur, a decision to stop using the pill or to change the brand of pill should be made only after three consecutive months of use. Occasionally, users develop high blood pressure that may require stopping the use of birth control pills.

Other side effects may include

- growth of pre-existing fibroid tumours of the uterus;
- an increase or decrease in hair growth, sex drive and appetite;
- skin pigmentation;
- headaches;
- Abnormal liver test, nausea, vomiting, severe pain or lump in the abdomen;
- rash; and/or
- vaginal infections.

Infrequently, there is a need to change contact lens prescription or an inability to use contact lenses.

A woman's menstrual period may be delayed after stopping birth control pills. There is no evidence that the use of the pill leads to a decrease in fertility. As mentioned, it is wise to delay starting a pregnancy for one menstrual period after stopping birth control pills.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		**Talk to your healthcare professional**		**Stop taking this drug and get immediate medical help**
		Only if severe	**In all cases**	
Common	Persistent sad mood			√
Uncommon	Sharp pain in the chest, coughing blood, or sudden shortness of breath			√
	Pain or swelling in the leg			√
	Crushing chest pain or heaviness			√

IMPORTANT: PLEASE READ

Symptom / effect		Talk to your healthcare professional		Stop taking this drug and get immedi ate medica l help
		Only if severe	In all cases	
	Sudden severe or worsening headache or vomiting, dizziness or fainting, disturbance of vision or speech, or weakness or numbness in an arm or leg			√
	Sudden partial or complete loss of vision			√
	Abdominal pain, nausea or vomiting or lump in the abdomen		√	
	Yellowing of the skin or eyes (jaundice)			√
	Unusual swelling of the extremities		√	
	Breast lumps		√	
	Unexpected (Abnormal) vaginal bleeding		√	

This is not a complete list of side effects. For any unexpected effects while taking OVIMA, contact your doctor or pharmacist.

HOW TO STORE IT

Store at controlled room temperature (15°C to 30°C). OVIMA 21 and OVIMA 28 should be protected from light once opened using the protective covering provided. Keep out of reach of children and pets.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about OVIMA 21 and OVIMA 28:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html). the manufacturer's website http://www.apotex.ca/products, or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

Date of Revision: January 30, 2026