

LOW-OGESTREL- norgestrel and ethinyl estradiol
RPK Pharmaceuticals, Inc.

Low-Ogestrel®

(Norgestrel and Ethinyl Estradiol Tablets USP, 0.3 mg/0.03 mg)

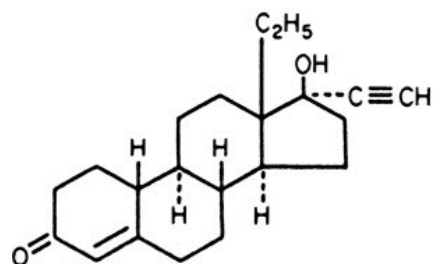
**WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR
EVENTS**

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs are contraindicated in women who are over 35 years of age and smoke [see *Contraindications*].

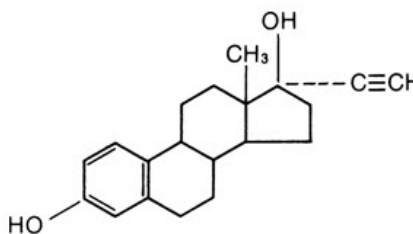
DESCRIPTION

Low-Ogestrel is a combination oral contraceptive containing the progestational compound norgestrel and the estrogenic compound ethinyl estradiol. Norgestrel is designated as (2) (\pm)-13 Ethyl-17-hydroxy-18,19-dinor-17 α -pregn-4-en-20-yn-3-one and ethinyl estradiol is designated as (19-nor-17 α -pregna-1,3,5 (10)-trien-20-yne-3,17-diol). Each white active Low-Ogestrel tablet contains 0.3 mg norgestrel and 0.03 mg ethinyl estradiol and the following inert ingredients: croscarmellose sodium, lactose, magnesium stearate, microcrystalline cellulose, and povidone.

Each peach placebo tablet contains only the following inert ingredients: anhydrous lactose, FD&C Yellow No. 6 Lake, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. Each pill pack contains 21 white active tablets and 7 peach inert tablets.



Norgestrel
C₂₁H₂₈O₂
M.W. 312.45



Ethinyl Estradiol
C₂₀H₂₄O₂
M.W. 296.40

CLINICAL PHARMACOLOGY

Mechanism of Action

Combined oral contraceptives (COCs) prevent pregnancy primarily by suppressing ovulation.

INDICATIONS AND USAGE

Low-Ogestrel is indicated for use by females of reproductive potential to prevent pregnancy. In a study of 1,287 women with a total of 11,085 cycles or 852.7 women-years of usage, the pregnancy rate in women age 15-40 years was approximately 1 pregnancy per 100 women-years of use.

CONTRAINDICATIONS

Low-Ogestrel is contraindicated in females who are known to have or develop the following conditions:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
 - Smoke, if over age 35
 - Have deep-vein thrombosis or pulmonary embolism, now or in the past
 - Have inherited or acquired coagulopathies
 - Have cerebrovascular disease
 - Have coronary artery disease
 - Have thrombotic valvular or thrombotic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease or atrial fibrillation)
 - Have uncontrolled hypertension
 - Have diabetes mellitus with vascular disease
 - Headaches with focal neurological symptoms or migraine headaches with aura
 - Women over age 35 with any migraine headaches
- Liver tumors, benign or malignant, or liver disease
- Undiagnosed abnormal uterine bleeding
- Pregnancy, because there is no reason to use COCs during pregnancy
- Current diagnosis of, or history of, breast cancer, which may be hormone-sensitive
- Hypersensitivity to any of the components of Low-Ogestrel

Women who are receiving Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT Elevations (see *Warnings, Risk of liver enzyme elevations with concomitant hepatitis c treatment*).

WARNINGS

1. Thromboembolic Disorders and Other Vascular Problems

- Stop Low-Ogestrel if an arterial thrombotic event or venous thromboembolic (VTE) event occurs.
- Stop Low-Ogestrel if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.
- If feasible, stop Low-Ogestrel at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE as well as during and following prolonged immobilization.
- Start Low-Ogestrel no earlier than 4 weeks after delivery, in women who are not

breastfeeding. The risk of postpartum VTE decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

- The use of COCs increases the risk of VTE. However, pregnancy increases the risk of VTE as much or more than the use of COCs. The risk of VTE in women using COCs is 3 to 9 cases per 10,000 woman-years. The risk of VTE is highest during the first year of use of COCs and when restarting hormonal contraception after a break of 4 weeks or longer. The risk of thromboembolic disease due to COCs gradually disappears after use is discontinued.
- Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes). This risk increases with age, particularly in women over 35 years of age who smoke.
- Use COCs with caution in women with cardiovascular disease risk factors.

2. Liver Disease

Impaired Liver Function

Do not use Low-Ogestrel in women with liver disease, such as acute viral hepatitis or severe (decompensated) cirrhosis of the liver [see *Contraindications*]. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded. Discontinue Low-Ogestrel if jaundice develops.

Liver Tumors

Low-Ogestrel is contraindicated in women with benign and malignant liver tumors [see *Contraindications*]. Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases/100,000 users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) COC users. However, the risk of liver cancers in COC users approaches less than one case per million users.

Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

During clinical trials with the Hepatitis C combination drug regimen that contains ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinyl estradiol-containing medications such as COCs. Discontinue Low-Ogestrel prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir [see *Contraindications*]. Low-Ogestrel can be restarted approximately 2 weeks following completion of treatment with the combination drug regimen.

3. High Blood Pressure

Low-Ogestrel is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease [see *Contraindications*]. For women with well-controlled hypertension, monitor blood pressure and stop Low-Ogestrel if blood

pressure rises significantly.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women with extended duration of use. The incidence of hypertension increases with increasing quantities of progestin.

4. Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users. Use of COCs may worsen existing gallbladder disease. A past history of COC-related cholestasis predicts an increased risk with subsequent COC use. Women with a history of pregnancy-related cholestasis may be at an increased risk for COC related cholestasis.

5. Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who take Low-Ogestrel. COCs may decrease glucose tolerance.

Consider alternative contraception for women with uncontrolled dyslipidemia. A small proportion of women will have adverse lipid changes while on COCs.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

6. Headache

If a woman taking Low-Ogestrel develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Low-Ogestrel if indicated.

Consider discontinuation of Low-Ogestrel in the case of increased frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event).

7. Bleeding Irregularities and Amenorrhea

Unscheduled Bleeding and Spotting

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different contraceptive product.

In 1,287 patients (pooled data from a number of studies), unscheduled bleeding was recorded in 15% of first cycles and by Cycle 12 was 5%. In total, 23% of subjects reported spotting, 20% reported unscheduled bleeding, and 2% reported change in menstrual flow at some point in the studies.

In the studies, 1.2% discontinued use of the product due to breakthrough bleeding and 1% discontinued due to spotting.

Amenorrhea and Oligomenorrhea

Women who use Low-Ogestrel may experience amenorrhea. A total of 9% of subjects in the studies reported amenorrhea in one or more cycles.

Some women may experience amenorrhea or oligomenorrhea after discontinuation of COCs, especially when such a condition was pre-existent.

If scheduled (withdrawal) bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

8. Depression

Carefully observe women with a history of depression and discontinue Low-Ogestrel if depression recurs to a serious degree.

9. Malignant Neoplasms

Breast Cancer

Low-Ogestrel is contraindicated in females who currently have or have had breast cancer because breast cancer may be hormonally sensitive [see *Contraindications*].

Epidemiology studies have not found a consistent association between use of combined oral contraceptives (COCs) and breast cancer risk. Studies do not show an association between ever (current or past) use of COCs and risk of breast cancer. However, some studies report a small increase in the risk of breast cancer among current or recent users (<6 months since last use) and current users with longer duration of COC use [see Postmarketing Experience].

Cervical Cancer

Some studies suggest that COC use has been associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

PRECAUTIONS

1. Effect on Binding Globulins

The estrogen component of COCs may raise the serum concentrations of thyroxine-binding globulin, sex hormone-binding globulin, and cortisol-binding globulin. The dose of replacement thyroid hormone or cortisol therapy may need to be increased.

2. Hereditary Angioedema

In females with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

3. Chloasma

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or

ultraviolet radiation while taking Low-Ogestrel.

4. Drug Interactions

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation

Do not co-administer Low-Ogestrel with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations (see *Warnings, Risk of liver enzyme elevations with concomitant hepatitis c treatment*).

Effects of Other Drugs on Combined Oral Contraceptives

Substances decreasing the plasma concentrations of COCs and potentially diminishing the efficacy of COCs

Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of COCs and potentially diminish the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate, rifabutin, rufinamide, aprepitant, and products containing St. John's wort. Interactions between hormonal contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Colesevelam

Colesevelam, a bile acid sequestrant, given together with a COC, has been shown to significantly decrease the AUC of EE. The drug interaction between the contraceptive and colesevelam was decreased when the two drug products were given 4 hours apart.

Substances increasing the plasma concentrations of COCs

Co-administration of atorvastatin or rosuvastatin and certain COCs containing EE increase AUC values for EE by approximately 20-25%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation. Concomitant administration of CYP3A4 inhibitors such as itraconazole, fluconazole, grapefruit juice or ketoconazole may increase plasma hormone concentrations.

Human immunodeficiency virus (HIV)/ Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors

Significant changes (increase or decrease) in the plasma concentrations of the estrogen and/or progestin have been noted when COCs are co-administered with some HIV protease inhibitors (decrease [e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos) amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir], or increase [e.g., indinavir and atazanavir/ritonavir] HCV protease inhibitors (decrease [e.g., nevirapine] or

increase [e.g., etravirine]).

Effects of Combined Oral Contraceptives on Other Drugs

COCs containing EE may inhibit the metabolism of other drugs (e.g., cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole) and increase their plasma concentrations. COCs have been shown to decrease plasma concentrations of acetaminophen, clofibric acid, morphine, salicylic acid, temazepam and lamotrigine. Significant decrease in the plasma concentration of lamotrigine has been shown, likely due to induction of lamotrigine glucuronidation.

This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentration of thyroid-binding globulin increases with use of COCs.

5. Interference with Laboratory Tests

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins.

6. Carcinogenesis

See **WARNINGS Section 2** and **WARNINGS Section 9**.

7. Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or nongenital birth defects (including cardiac anomalies and limb reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

Discontinue Low-Ogestrel use if pregnancy is confirmed.

Do not administer COCs to induce withdrawal bleeding as a test for pregnancy. Do not use COCs during pregnancy to treat threatened or habitual abortion.

8. Nursing Mothers

Advise the nursing mother to use other forms of contraception, when possible, until she has weaned her child. COCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

9. Pediatric Use

Safety and efficacy of Low-Ogestrel tablets have been established in women of reproductive age. Efficacy is expected to be the same for post-pubertal adolescents under the age of 16 and for users 16 years and older. Use of Low-Ogestrel before menarche is not indicated.

10. Geriatric Use

Low-Ogestrel has not been studied in postmenopausal women and is not indicated in this population.

11. Information for the Patient

See FDA-approved patient labeling (Patient Information and Instructions for Use). Counsel patients about the following information:

- Cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs [see *Boxed Warning*].
- Increased risk of VTE compared to non-users of COCs is greatest after initially starting a COC or restarting (following a 4-week or greater pill-free interval) the same or a different COC.
- Low-Ogestrel does not protect against HIV infection and other sexually transmitted infections.
- Low-Ogestrel is not to be used during pregnancy; if pregnancy occurs during use of Low-Ogestrel, instruct the patient to stop further use.
- Take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event tablets are missed.
- Use a back-up or alternative method of contraception when enzyme inducers are used with Low-Ogestrel.
- COCs may reduce breast milk production; this is less likely to occur if breastfeeding is well established.
- Women who start COCs postpartum, and who have not yet had a period, should use an additional method of contraception until they have taken an active tablet for 7 consecutive days.
- Amenorrhea may occur. Consider pregnancy in the event of amenorrhea at the time of the first missed period. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles.

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions (see *Warnings* section for additional information) has been associated with the use of oral contraceptives:

- Serious cardiovascular events and stroke [see *Boxed Warning*]
- Vascular events
- Liver disease

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the

clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of Low-Ogestrel was evaluated in 1,343 healthy women of child-bearing potential who participated in 9 clinical trials and received at least one dose of Low-Ogestrel for contraception. Subjects were exposed for a total of 11,085 cycles, with 429 women completing one year of exposure. Subjects ranged in age from 15-40 years. Demographics were 69% Caucasian, 28% Black, and 3% other.

Common Adverse Reactions ($\geq 2\%$ of women):

- Weight increase (11%)
- Cervical erosion (9%)
- Weight decrease (6%)
- Acne (4%)
- Dysmenorrhea (4%)
- Vaginal discharge (4%)
- Abdominal pain, cramps, and bloating (3%)
- Appetite increase (3%)
- Depression (3%)
- Nervousness (3%)
- Chloasma/melasma (2%)
- Fatigue (2%)
- Varicose veins, aggravation of (2%)

A total of 8% of subjects discontinued the trials prematurely due to an adverse reaction, most commonly due to unscheduled bleeding, spotting, headache (including migraine), nausea, acne, changes in menstrual flow, weight increase, nervousness, high blood pressure, and depression.

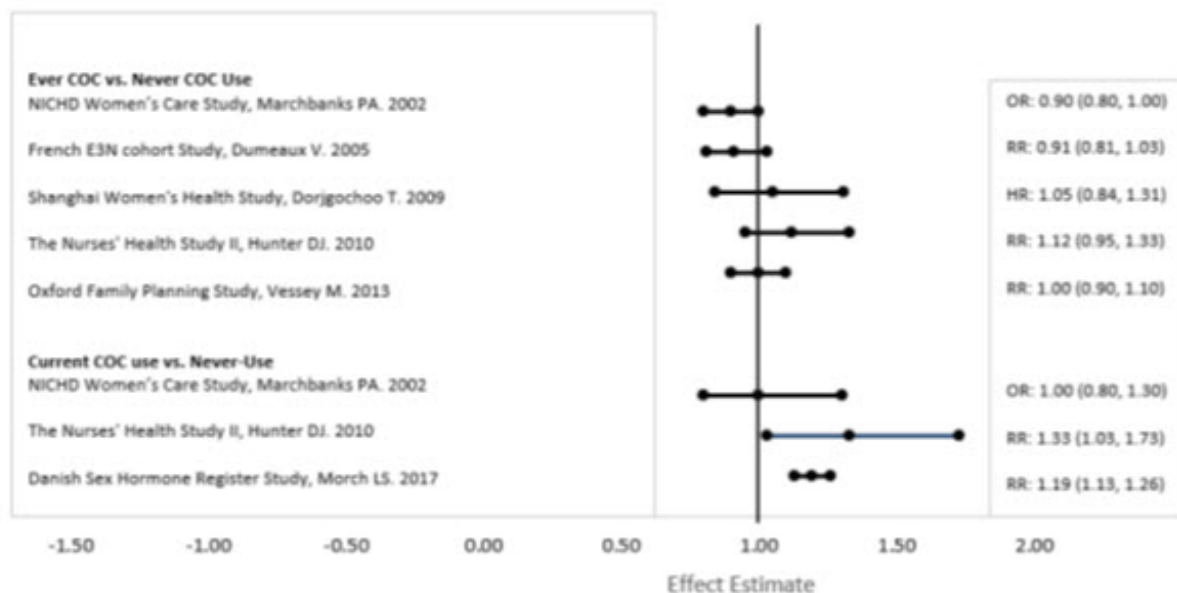
Postmarketing Experience

Five studies that compared breast cancer risk between ever-users (current or past use) of COCs and never-users of COCs reported no association between ever use of COCs and breast cancer risk, with effect estimates ranging from 0.90 - 1.12 (Figure 1).

Three studies compared breast cancer risk between current or recent COC users (<6 months since last use) and never users of COCs (Figure 1). One of these studies reported no association between breast cancer risk and COC use. The other two studies found an increased relative risk of 1.19 - 1.33 with current or recent use. Both of these studies found an increased risk of breast cancer with current use of longer duration, with relative risks ranging from 1.03 with less than one year of COC use to approximately 1.4 with more than 8-10 years of COC use.

Figure 1: Risk of Breast Cancer with Combined Oral Contraceptive Use

Relevant Studies of Risk of Breast Cancer with Combined Oral Contraceptives



RR = relative risk; OR = odds ratio; HR = hazard ratio. "ever COC" are females with current or past COC use; "never COC use" are females that never used COCs.

The following additional adverse drug reactions have been reported from worldwide postmarketing experience with Low-Ogestrel. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Arterial Events: Arterial thromboembolism, Myocardial infarction, Cerebral hemorrhage

Eye Disorder: Optic neuritis, which may lead to partial or complete loss of vision, Intolerance to contact lenses, Change (steepening) in corneal curvature

Gastrointestinal Disorders: Colitis, Nausea, Pancreatitis

Hepatobiliary Disorders: Gallbladder disease, Cholestatic jaundice, Budd-Chiari syndrome

Immune System Disorders: Anaphylactic/anaphylactoid reactions, including urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms

Metabolism and Nutrition Disorders: Carbohydrate and lipid effects, Porphyria, exacerbation of Porphyria

Neoplasms, Benign, Malignant, and Unspecified: Carcinoma of the reproductive organs and breasts, Hepatic neoplasia (including hepatic adenomas or benign liver tumors)

Psychiatric Disorders: Mood changes

Reproductive System and Breast Disorders: Temporary infertility after discontinuation of treatment, Changes in libido, Vaginitis, including candidiasis; Breast secretion

Skin and Subcutaneous Tissue Disorders: Melasma/chloasma, which may persist; Erythema multiforme, Erythema nodosum, Hemorrhagic eruption, Hirsutism

Vascular Events: Venous thrombosis, Pulmonary embolism, Cerebral thrombosis, Mesenteric thrombosis, Retinal vascular thrombosis

OVERDOSAGE

There have been no reports of serious ill effects from overdosage of oral contraceptives, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, Low-Ogestrel (norgestrel and ethinyl estradiol tablets) must be taken exactly as directed and at intervals not exceeding 24 hours. The dosage of Low-Ogestrel is one white tablet daily for 21 consecutive days, followed by one peach inert tablet daily for 7 consecutive days, according to prescribed schedule. It is recommended that Low-Ogestrel tablets be taken by mouth at the same time each day.

How to Start Low-Ogestrel

Consider the possibility of ovulation and conception prior to initiation of medication.

Instruct the patient to begin taking Low-Ogestrel on the first Sunday after the onset of menstruation. If menstruation begins on a Sunday, the first tablet (white) is taken that day. The patient should take one white tablet daily for 21 consecutive days followed by one peach inert tablet daily for 7 consecutive days. Withdrawal bleeding will usually occur within 3 days following discontinuation of white tablets and may not have finished before the next pack is started. During the first cycle, the patient should not rely on Low-Ogestrel for contraception until a white tablet has been taken daily for 7 consecutive days and she should use a non-hormonal back-up method of birth control during those 7 days.

After the first cycle of use

The patient is to begin her next and all subsequent 28-day courses of tablets on the same day of the week (Sunday) on which she began her first course, following the same schedule: 21 days of white tablets, followed by 7 days of peach inert tablets. If in any cycle the patient starts tablets later than the proper day, instruct her to protect herself against pregnancy by using a non-hormonal back-up method of birth control until she has taken a white tablet daily for 7 consecutive days.

Switching from another hormonal method of contraception

- When the patient is switching from a 21-day regimen of tablets, instruct her to wait 7 days after her last tablet before she starts Low-Ogestrel. She will probably experience withdrawal bleeding during that week. Instruct her not to let more than 7 days pass after her previous 21-day regimen before she starts Low-Ogestrel.
- When the patient is switching from a 28-day regimen of tablets, instruct her to start her first pack of Low-Ogestrel on the day after her last tablet. She should not wait any days between packs.
- The patient may switch any day from a progestin-only pill and should begin Low-Ogestrel the next day. If switching from an implant or injection, instruct the patient to start Low-Ogestrel on the day of implant removal or the day the next injection would be due. If switching from a contraceptive vaginal ring or transdermal patch instruct

the patient to start Low-Ogestrel on the day they would have inserted the next ring or applied the next patch. If switching from an Intrauterine Device (IUD) or Intrauterine System (IUS), instruct the patient to start Low-Ogestrel on the day of IUD/IUS removal. If the IUD/IUS is not removed on the first day of the patient's menstrual cycle, instruct her to use a non-hormonal back-up method of birth control for the first 7 days of tablet-taking.

Use after pregnancy, abortion, or miscarriage

- Initiate Low-Ogestrel no earlier than day 28 postpartum in the nonlactating mother or after a second-trimester abortion due to the increased risk for thromboembolism (see *Contraindications, Warnings and Precautions* concerning thromboembolic disease). Advise the patient to use a non-hormonal back-up method for the first 7 days of tablet-taking.
- Low-Ogestrel may be initiated immediately after a first-trimester abortion or miscarriage. If the patient starts Low-Ogestrel immediately, back-up contraception is not needed.

If spotting or breakthrough bleeding occurs

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

Missed Tablets

The possibility of ovulation and pregnancy increases with each successive day that scheduled white tablets are missed. If withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed schedule (if she missed one or more tablets or started taking them on a day later than she should have), consider the probability of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

For additional patient instructions regarding missed tablets, see the **WHAT TO DO IF YOU MISS PILLS** section in *FDA-Approved Patient Labeling* below.

Advice in Case of Gastrointestinal Disturbances

In case of severe vomiting or diarrhea, absorption may not be complete and additional contraceptive measures should be taken. If vomiting or diarrhea occurs within 3 to 4 hours after taking an active tablet, handle this as a missed tablet [*see FDA-Approved Patient Labeling*].

HOW SUPPLIED

Low-Ogestrel[®] Tablets (0.3 mg norgestrel and 0.03 mg ethinyl estradiol) are available in cartons of 6 dispensers (**NDC 51862-564-06**), each containing 28 tablets as follows:

- 21 white, unscored, round active tablets debossed "WATSON" on one side and "847" on the other side.
- 7 peach, unscored, round inert tablets debossed "WATSON" on one side and "P1" on

the other side.

Store at 20°C to 25°C (68°F to 77°F) [See USP controlled room temperature].

Distributed by:

Mayne Pharma

Greenville, NC 27834

2000014486

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**FDA-Approved Patient Labeling Low-Ogestrel [Lo-Ogest-rell]
(norgestrel and ethinyl estradiol tablets)**

What is the most important information I should know about Low-Ogestrel?

Do not use Low-Ogestrel if you smoke cigarettes and are over 35 years old.

Smoking increases your risk of serious cardiovascular side effects from hormonal birth control pills, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

What is Low-Ogestrel?

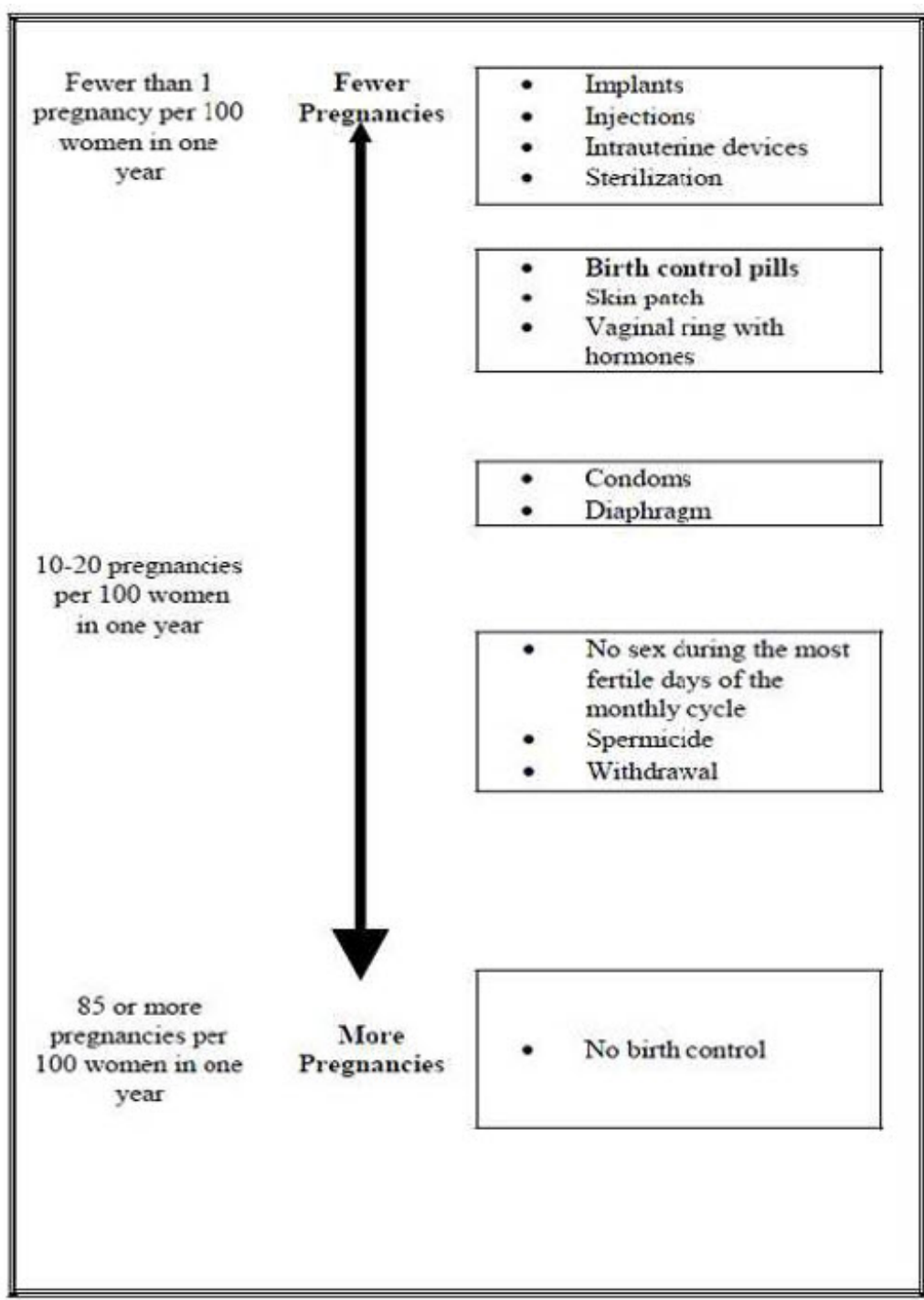
Low-Ogestrel is a birth control pill (oral contraceptive) used by women to prevent pregnancy.

How does Low-Ogestrel work for contraception?

Your chance of getting pregnant depends on how well you follow the directions for taking your birth control pills. The better you follow the directions, the less chance you have of getting pregnant.

Based on the results of clinical studies, about 1 out of 100 women may get pregnant during the first year they use Low-Ogestrel.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



Who should not take Low-Ogestrel?

Do not take Low-Ogestrel if you:

- smoke and are over 35 years old
- had blood clots in the legs, arms, lungs, or eyes
- had a problem with your blood that makes it clot more than normal
- have certain heart valve problems or irregular heart beat that increases your risk of having blood clots
- had a stroke
- had a heart attack
- have high blood pressure that cannot be controlled by medicine
- have diabetes with kidney, eye, nerve or blood vessel damage
- have certain kinds of severe migraine headaches with aura, numbness, weakness or

- changes in vision, or have any migraine headaches if you are over 35 years of age
- have liver problems, including liver tumors
- have any unexplained vaginal bleeding
- are pregnant
- have or had breast cancer or any cancer that is sensitive to female hormones
- have a known allergy or hypersensitivity to any of the components of Low-Ogestrel (norgestrel and ethinyl estradiol tablets)

You should not take the pill if you take any Hepatitis C drug combination containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. This may increase levels of the liver enzyme "alanine aminotransferase" (ALT) in the blood.

If any of these conditions happen while you are taking Low-Ogestrel, stop taking Low-Ogestrel right away and talk to your healthcare provider. Use non-hormonal contraception when you stop taking Low-Ogestrel.

What should I tell my healthcare provider before taking Low-Ogestrel?

Tell your healthcare provider if you:

- are pregnant or think you may be pregnant
- are depressed now or have been depressed in the past
- had yellowing of your skin or eyes (jaundice) caused by pregnancy (cholestasis of pregnancy)
- have a condition called hereditary angioedema
- are breastfeeding or plan to breastfeed. Low-Ogestrel may decrease the amount of breast milk you make. A small amount of the hormones in Low-Ogestrel may pass into your breast milk. Talk to your healthcare provider about the best birth control method for you while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

Low-Ogestrel may affect the way other medicines work, and other medicines may affect how well Low-Ogestrel works.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take Low-Ogestrel?

Read the Instructions for Use at the end of this Patient Information.

What are the possible serious side effects of Low-Ogestrel?

- **Like pregnancy, Low-Ogestrel may cause serious side effects, including blood clots in your lungs, heart attack, or a stroke that may lead to death.**
- **Some other examples of serious blood clots include blood clots in the legs or eyes.**

Serious blood clots can happen especially if you smoke, are obese, or are older than 35 years of age.

Serious blood clots are more likely to happen when you:

- first start taking birth control pills
- restart the same or different birth control pills after not using them for a month or more

Call your healthcare provider or go to a hospital emergency room right away if you have:

- leg pain that will not go away
- sudden severe shortness of breath
- sudden change in vision or blindness
- chest pain
- a sudden, severe headache unlike your usual headaches
- weakness or numbness in your arm or leg
- trouble speaking

Other serious side effects include:

- **liver problems, including:**
 - rare liver tumors
 - jaundice (cholestasis), especially if you previously had cholestasis of pregnancy. Call your healthcare provider if you have yellowing of your skin or eyes.
- **high blood pressure**
- **gallbladder problems**
- **changes in the sugar and fat (cholesterol and triglycerides) levels in your blood**
- **new or worsening headaches including migraine headaches**
- **depression**
- **possible cancer in your breast and cervix**
- **swelling of your skin especially around your mouth, eyes, and in your throat (angioedema).** Call your healthcare provider if you have a swollen face, lips, mouth tongue or throat, which may lead to difficulty swallowing or breathing. Your chance of having angioedema is higher if you have a history of angioedema.

What are the most common side effects of Low-Ogestrel?

- menstrual complaints, including unscheduled bleeding and spotting
- nausea
- headache (including migraine)
- weight increase or decrease
- cervical erosion
- acne
- menstrual cramps
- vaginal discharge
- stomach pain, discomfort, and gas
- increase in appetite
- depression
- nervousness
- dark areas on your face
- fatigue
- worsening of varicose veins

These are not all the possible side effects of **Low-Ogestrel**. For more information, ask your healthcare provider or pharmacist.

You may report side effects to the FDA at 1-800-FDA-1088.

What else should I know about taking Low-Ogestrel?

- If you are scheduled for any lab tests, tell your healthcare provider you are taking Low-Ogestrel. Certain blood tests may be affected by Low-Ogestrel.
- Low-Ogestrel does not protect against HIV infection (AIDS) and other sexually transmitted infections.

How should I store Low-Ogestrel?

- Store Low-Ogestrel at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep Low-Ogestrel and all medicines out of the reach of children.
- Store away from light.

General information about the safe and effective use of Low-Ogestrel:

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use Low-Ogestrel for a condition for which it was not prescribed. Do not give Low-Ogestrel to other people, even if they have the same symptoms that you have.

This Patient Information summarizes the most important information about Low-Ogestrel. You can ask your pharmacist or healthcare provider for information about Low-Ogestrel that is written for health professionals.

For more information, call 1-844-825-8500.

Do birth control pills cause cancer?

There may be slight increases in the risk of breast cancer among current users of hormonal birth control pills with longer duration of use of 8 years or more.

Women who use birth control pills may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

What if I want to become pregnant?

You may stop taking the pill whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop taking the pill.

What should I know about my period when taking Low-Ogestrel?

Your periods may be lighter and shorter than usual. Some women may miss a period. Irregular vaginal bleeding or spotting may happen while you are taking Low-Ogestrel, especially during the first few months of use. This usually is not a serious problem. It is important to continue taking your pills on a regular schedule to prevent a pregnancy.

What are the ingredients in Low-Ogestrel?

Active ingredients:

Each white pill contains norgestrel and ethinyl estradiol.

Inactive ingredients:

White pills: croscarmellose sodium, lactose, magnesium stearate, microcrystalline cellulose, and povidone.

Peach pills: anhydrous lactose, FD&C Yellow No. 6 Lake, lactose monohydrate, magnesium stearate, and microcrystalline cellulose.

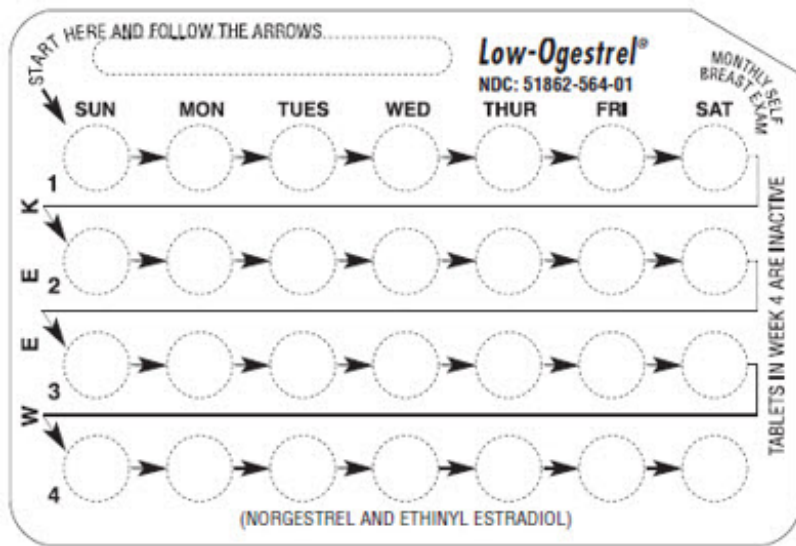
Instructions for Use

Important Information about taking Low-Ogestrel

- Take **1** pill every day at the same time. Take the pills in the order directed on your pill dispenser.
- Do not skip your pills, even if you do not have sex often. If you miss pills (including starting the pack late) **you could get pregnant**. The more pills you miss, the more likely you are to get pregnant.
- If you have trouble remembering to take Low-Ogestrel, talk to your healthcare provider.
- When you first start taking Low-Ogestrel, spotting or light bleeding in between your periods may occur. Contact your healthcare provider if this does not go away after a few months.
- You may feel sick to your stomach (nauseous), especially during the first few months of taking Low-Ogestrel. If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If your nausea does not go away, call your healthcare provider.
- Missing pills can also cause spotting or light bleeding, even when you take the missed pills later. On the days you take 2 pills to make up for missed pills (see **WHAT TO DO IF YOU MISS PILLS?** below), you could also feel a little sick to your stomach.
- It is not uncommon to miss a period. However, if you miss a period and have not taken Low-Ogestrel according to directions, or miss 2 periods in a row, or feel like you may be pregnant, call your healthcare provider. If you have a positive pregnancy test, you should stop taking Low-Ogestrel.
- If you have vomiting or diarrhea within 3–4 hours of taking your pill, take another pill of the same color from your extra pill dispenser. If you do not have an extra pill dispenser, take the next pill in the dispenser you are currently using. Continue taking all your remaining pills in order. Start the first pill of your next pill dispenser the day after finishing your current pill dispenser. This will be 1 day earlier than originally scheduled. Continue on your new schedule.
- If you have vomiting or diarrhea for more than 1 day, your birth control pills may not work as well. Use an additional birth control method, like condoms or spermicide, until you check with your healthcare provider.
- Stop taking Low-Ogestrel at least 4 weeks before you have major surgery and do not restart after the surgery without asking your healthcare provider. Be sure to use another form of contraception (like condoms or spermicide) during this time period.

BEFORE YOU START TAKING Low-Ogestrel

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL. It is important to take it at about the same time every day.
2. LOOK AT YOUR PILL PACK:
The pill pack has 21 "active" white pills (with hormones) to take for 3 weeks, followed by 1 week of reminder peach pills (without hormones).
3. FIND:
 - 1) where on the pack to start taking pills, and
 - 2) in what order to take the pills (follow the arrows).



4. BE SURE YOU HAVE READY AT ALL TIMES:

- Another kind of birth control (such as condoms or spermicide) to use as a back-up in case you miss pills
- An extra, full pill pack

WHEN TO START THE FIRST PACK OF PILLS

SUNDAY START:

1. Take the first "active" white pill of the first pack on the *Sunday after your period starts*, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. Use a *non-hormonal method of birth control* (such as condoms or spermicide) as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days).

WHAT TO DO DURING THE MONTH

1. Take one pill at the same time every day until the pack is empty.
Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).
Do not skip pills even if you do not have sex very often.
2. When you finish a pack:
Start the next pack on the day after your last "reminder" pill. Do not wait any days between packs.

IF YOU SWITCH FROM ANOTHER BRAND OF COMBINATION PILLS:

If your previous brand had 21 pills: Wait 7 days to start taking Low-Ogestrel. You will probably have your period during that week. Ideally, be sure that no more than 7 days pass between the 21-day pack and taking the first white Low-Ogestrel pill ("active" with hormone). If you start Low-Ogestrel more than 7 days after taking the last pill of your previous contraceptive, you must use a non-hormonal back-up method of birth control during the first 7 days of Low-Ogestrel use.

If your previous brand had 28 pills: Start taking the first white Low-Ogestrel pill ("active" with hormone) on the day after your last reminder pill. Ideally, do not wait any days

between packs. If you do skip any days between the last pill of your previous contraceptive and starting Low-Ogestrel, you must use a non-hormonal back-up method of birth control during the first 7 days of Low-Ogestrel use.

IF YOU SWITCH FROM ANOTHER TYPE OF BIRTH CONTROL METHOD:

If you were previously taking a progestin-only PILL: You may switch to Low-Ogestrel on any day from a progestin-only pill and should start taking the first white Low-Ogestrel pill ("active" with hormone) the day after you take your last progestin-only pill. In addition, use a non-hormonal back-up method of birth control for the first 7 days of tablet-taking.

If you are switching from a contraceptive vaginal ring or transdermal patch: Start taking the first white Low-Ogestrel pill ("active" with hormone) on the day that you would have inserted a new ring or applied a new patch.

If you are switching from a contraceptive implant: Start taking the first white Low-Ogestrel pill ("active" with hormone) on the day that the implant is removed.

If you are switching from a contraceptive injection: Start taking the first white Low-Ogestrel pill ("active" with hormone) on the day that the next contraceptive injection is due.

If you are switching from an Intrauterine device (IUD) or Intrauterine system (IUS): Start taking the first white Low-Ogestrel pill ("active" with hormone) on the day the IUD/IUS is removed. If your IUD/IUS is removed on the first day of your period you do not need to use an additional non-hormonal back up method of birth control. If the IUD/IUS is removed on any other day, use a non-hormonal back-up method of birth control for the first 7 days of tablet-taking.

WHAT TO DO IF YOU MISS PILLS

Low-Ogestrel may not be as effective if you miss white "active" pills, and particularly if you miss the first few or the last few white "active" pills in a pack.

If you **MISS 1** white "active" pill:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.
2. You **could become pregnant** if you have sex in the 7 days after you restart your pills. You **MUST** use a non-hormonal birth control method (such as condoms or spermicide) as a back-up for those 7 days.

If you **MISS 2** white "active" pills in a row in **WEEK 1 OR WEEK 2** of your pack:

1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You **could become pregnant** if you have sex in the 7 days after you restart your pills. You **MUST** use a non-hormonal birth control method (such as condoms or spermicide) as a back-up for those 7 days.

If you **MISS 2** white "active" pills in a row in **THE 3rd WEEK:**

1. Keep taking 1 pill every day until Sunday.
On Sunday, **throw out** the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss

your period 2 months in a row, call your healthcare provider because you might be pregnant.

3. You **could become pregnant** if you have sex in the *7 days* after you restart your pills. You **MUST** use a non-hormonal birth control method (such as condoms or spermicide) as a back-up for those 7 days.

If you **MISS 3 OR MORE** white "active" pills in a row (during the first 3 weeks):

1. Keep taking 1 pill every day until Sunday.

On Sunday, **throw out** the rest of the pack and start a new pack of pills that same day.

2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your healthcare provider because you might be pregnant.

3. You **could become pregnant** if you have sex in the *7 days* after you restart your pills. You **MUST** use a non-hormonal birth control method (such as condoms or spermicide) as a back-up for those 7 days.

If you forget any of the 7 peach "reminder" pills in Week 4:

Throw away the pills you missed.

Keep taking 1 pill each day until the pack is empty.

You do not need a back-up non-hormonal birth control method if you start your next pack on time.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED

Use a **back-up non-hormonal birth control method** anytime you have sex. **Keep taking one pill each day** until you can reach your healthcare provider.

Distributed by:

Mayne Pharma
Greenville, NC 27834

2000014485
Revised 02/2022

Low-Ogestrel Tablets 28-Day Regimen

Box Label:
 NDC# 5182-0664-01
 LIST# 5182-0664-01
LOW-OGESTREL TABLETS 28-DAY REGIMEN
 28 Tablets
 LOT# 17299-029
 EXP DATE: 12-31-2018
 Shape & Color: **Stakings**
 PEACH w/WHITE P-41 WATSON (R)
 ROUND TABLET
 EACH WHITE TABLET CONTAINS NORGESTREL 0.020 mg AND ETHINYL DIESTRADIOL 0.020 mg. EACH PEACH TABLET CONTAINS INERT INGREDIENTS.
 PATIENT NAME: _____
LOW-OGESTREL TABLETS 28 DAY
 MAYNE PHARMA, Inc. Ref# 173550721000 ITEM# 1637 1637-1
TAKE 1 TABLET DAILY AS DIRECTED.
 CLINIC NAME GOES HERE
 IMPORTANT: READ PATIENT INFORMATION SHEET CAREFULLY BEFORE USING. TAKE ONLY AS DIRECTED BY YOUR PRESCRIBER.
 173550721000

Blister Pack Label:
 1 TAB DAILY LD
 LOT# 17299-029 EXP 12-31-2018
 Ref# 173550721 - 000 FCA- 1637
 28 ea LOW-OGESTREL TABLETS 28 DAY
 N# 173550721000 ITEM# 1637

Label:
LOW-OGESTREL TABLETS 28-DAY REGIMEN
 28 Tablets
 DISCARD BY 12-31-2018
 BILLING NDC# 5182-0664-01 NDC# 5182-0664-01
 Ref# 173550721 - 000 Ref# 173550721 - 000
 28 ea LOW-OGESTREL TABLETS 28 DAY 28 ea LOW-OGESTREL TABLETS 28 DAY
 BILLING NDC# 5182-0664-01
 Ref# 173550721 - 000
 28 ea LOW-OGESTREL TABLETS 28 DAY

LOW-OGESTREL

norgestrel and ethinyl estradiol kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:53002-1637(NDC:51862-564)
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Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:53002-1637-6	6 in 1 PACKAGE	09/01/2017	
1		1 in 1 BLISTER PACK; Type 0: Not a Combination Product		
2	NDC:53002-1637-3	3 in 1 PACKAGE	09/01/2017	
2		1 in 1 BLISTER PACK; Type 0: Not a Combination Product		
3	NDC:53002-1637-1	1 in 1 PACKAGE	09/01/2017	
3		1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1		21
Part 2		7

Part 1 of 2

LOW-OGESTREL

norgestrel and ethinyl estradiol tablet

Product Information

Route of Administration	ORAL
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Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ETHINYL ESTRADIOL (UNII: 423D2T571U) (ETHINYL ESTRADIOL - UNII:423D2T571U)	ETHINYL ESTRADIOL	0.03 mg
NORGESTREL (UNII: 3J8Q1747Z2) (NORGESTREL - UNII:3J8Q1747Z2)	NORGESTREL	0.3 mg

Inactive Ingredients

Ingredient Name	Strength
CROSCARMELOSE SODIUM (UNII: M28OL1HH48)	
LACTOSE, UNSPECIFIED FORM (UNII: J2B2A4N98G)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	

Product Characteristics

Color	WHITE	Score	no score
Shape	ROUND	Size	6mm
Flavor		Imprint Code	847;Watson
Contains			

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075288	08/03/2016	

Part 2 of 2

INERT

inert tablet

Product Information

Route of Administration	ORAL
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Inactive Ingredients

Ingredient Name	Strength
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	

Product Characteristics

Color	ORANGE (peach)	Score	no score
Shape	ROUND	Size	6mm
Flavor		Imprint Code	P1;Watson
Contains			

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075288	08/03/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075288	08/03/2016	

Labeler - RPK Pharmaceuticals, Inc. (147096275)

Establishment

Name	Address	ID/FEI	Business Operations
RPK Pharmaceuticals, Inc.		147096275	RELABEL(53002-1637) , REPACK(53002-1637)

Revised: 6/2023

RPK Pharmaceuticals, Inc.