Norgestimate and Ethinyl Estradiol Tablets USP

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Norgestimate and Ethinyl Estradiol Tablets USP safely and effectively. See full prescribing information for Norgestimate and Ethinyl Estradiol Tablets USP.

Norgestimate and Ethinyl Estradiol Tablets USP, for oral use
Initial U.S. Approval: 1989

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning.

- **Norgestimate and Ethinyl Estradiol Tablets USP are contraindicated in women over 35 years old who smoke. (4)**
- **Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. (4)**

INDICATIONS AND USAGE

Norgestimate and Ethinyl Estradiol Tablets USP are estrogen/progestin COCs, indicated for use by women to prevent pregnancy. (1.1)

Norgestimate and Ethinyl Estradiol Tablets USP are also indicated for the treatment of moderate acne vulgaris in females at least 15 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche.

Norgestimate and Ethinyl Estradiol Tablets USP should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control. (1.2)

DOSAGE AND ADMINISTRATION

- Take one tablet daily by mouth at the same time every day. (2.2)
- Take tablets in the order directed on the blister pack. (2.2)
- Do not skip or delay tablet intake. (2.2)

DOSAGE FORMS AND STRENGTHS

Norgestimate and Ethinyl Estradiol Tablets USP (0.25 mg/0.035 mg) consist of 28 round tablets in the following order (3):

- 21 dark blue tablets each containing 0.25 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 white tablets (inert)

Norgestimate and Ethinyl Estradiol Tablets USP (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg) consist of 28 round tablets in the following order (3):

- 7 light blue tablets each containing 0.18 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 medium blue tablets each containing 0.215 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 dark blue tablets each containing 0.25 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 white tablets (inert)

CONTRAINDICATIONS

- A high risk of arterial or venous thrombotic diseases (4)
- Liver tumors or liver disease (4)
- Undiagnosed abnormal uterine bleeding (4)
- Pregnancy (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)

WARNINGS AND PRECAUTIONS

- Thromboembolic Disorders and Other Vascular Problems: Stop Norgestimate and Ethinyl Estradiol Tablets USP if a thrombotic event occurs. Stop at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- Liver disease: Discontinue Norgestimate and Ethinyl Estradiol Tablets USP if jaundice occurs. (5.2)
- High blood pressure: If used in women with well-controlled hypertension, monitor blood pressure and stop Norgestimate and Ethinyl Estradiol Tablets USP if blood pressure rises significantly. (5.3)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking Norgestimate and Ethinyl Estradiol Tablets USP. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.5)
- Headache: Evaluate significant change in headaches and discontinue Norgestimate and Ethinyl Estradiol Tablets USP if indicated. (5.6)
- Bleeding Irregularities and Amenorrhea: Evaluate irregular bleeding or amenorrhea. (5.7)

ADVERSE REACTIONS

The most common adverse reactions reported during clinical trials (≥2%) were:

Norgestimate and Ethinyl Estradiol Tablets USP (0.25 mg/0.035 mg): headache/migraine, abdominal/gastrointestinal pain, vaginal infection, genital discharge, breast issues (including breast pain, discharge, and enlargement), mood disorders (including depression and mood altered), flatulence, nervousness, rash. (6.1)

Norgestimate and Ethinyl Estradiol Tablets USP (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg): headache/migraine, breast issues (including breast pain, enlargement, and discharge), vaginal infection, abdominal/gastrointestinal pain, mood disorders (including mood alteration and depression), genital discharge, changes in weight (including weight increased or decreased). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Akorn, Inc. at 1-800-932-5676 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs. (7.1)

USE IN SPECIFIC POPULATIONS

Nursing mothers: Not recommended; can decrease milk production. (8:3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/16

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

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 (4)*].

1 INDICATIONS AND USAGE

1.1 Oral Contraceptive

Norgestimate and Ethinyl Estradiol Tablets USP are indicated for use by females of reproductive potential to prevent pregnancy *[see Clinical Studies (14)*].

1.2 Acne

Norgestimate and Ethinyl Estradiol Tablets USP, (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg) are indicated for the treatment of moderate acne vulgaris in females at least 15 years of age, who have no known contraindications to oral

contraceptive therapy and have achieved menarche. Norgestimate and Ethinyl Estradiol Tablets USP, (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg) should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control [*see Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

2.1 How to Start Norgestimate and Ethinyl Estradiol Tablets USP

Norgestimate and Ethinyl Estradiol Tablets USP are dispensed in a blister pack [*see How Supplied/Storage and Handling (16)*].

Norgestimate and Ethinyl Estradiol Tablets USP may be started using either a Day 1 start or a Sunday start (see Table 1). For the first cycle of a Sunday Start regimen, an additional method of contraception should be used until after the first 7 consecutive days of administration.

2.2 How to Take Norgestimate and Ethinyl Estradiol Tablets USP

Table 1: Instructions for Administration of Norgestimate and Ethinyl Estradiol Tablets USP

Starting COCs in women not currently using hormonal contraception (Day 1 Start or Sunday Start) **Important:** Consider the possibility of ovulation and conception prior to initiation of this product. **Tablet Color:** • Norgestimate and Ethinyl Estradiol Tablets USP, (0.25 mg/ 0.035 mg) active tablets are dark blue (Day 1 to Day 21). • Norgestimate and Ethinyl Estradiol Tablets USP, (0.18 mg/0.035 mg, 0.215 mg/ 0.035 mg and 0.25 mg/ 0.035 mg) active tablets are light blue (Day 1 to Day 7), medium blue (Day 8 to Day 15) and dark blue (Day 16 to Day 21). • Norgestimate and Ethinyl Estradiol Tablets USP both have white inactive tablets (Day 22 to Day 28)	**Day 1 Start:** • Take first active tablet without regard to meals on the first day of menses. • Take subsequent active tablets once daily at the same time each day for a total of 21 days. • Take one white inactive tablet daily for 7 days and at the same time of day that active tablets were taken. • Begin each subsequent pack on the same day of the week as the first cycle pack (i.e., on the day after taking the last inactive tablet) **Sunday Start:** • Take first active tablet without regard to meals on the first Sunday after the onset of menses. **Due to the potential risk of becoming pregnant, use additional non-hormonal contraception (such as condoms and spermicide) for the first seven days of the patient's first cycle pack of Norgestimate and Ethinyl Estradiol Tablets USP.** • Take subsequent active tablets once daily at the same time each day for a total of 21 days. • Take one **white** inactive tablet daily for the following 7 days and at the same time of day that active tablets were taken. • Begin each subsequent pack on the same day of the week as the first cycle pack (i.e., on the Sunday after taking the last inactive tablet) and additional non-hormonal contraceptive is not needed.
Switching to Norgestimate and Ethinyl Estradiol Tablets USP from another oral contraceptive	Start on the same day that a new pack of the previous oral contraceptive would have started.
Switching from another contraceptive method to Norgestimate and Ethinyl Estradiol Tablets USP	**Start Norgestimate and Ethinyl Estradiol Tablets USP:**
• **Transdermal patch**	• On the day when next application would have been scheduled
• **Vaginal ring**	• On the day when next insertion would have been scheduled
• **Injection**	• On the day when next injection would have been scheduled
• **Intrauterine contraceptive**	• On the day of removal • If the IUD is not removed on first day of the patient's menstrual cycle, additional non-hormonal contraceptive (such as condoms and spermicide) is needed for the first seven days of the first cycle pack.
• **Implant**	• On the day of removal
Complete instructions to facilitate patient counseling on proper tablet usage are located in the FDA-Approved Patient Labeling.	

Starting Norgestimate and Ethinyl Estradiol Tablets USP after Abortion or Miscarriage

First-trimester

- After a first-trimester abortion or miscarriage, Norgestimate and Ethinyl Estradiol Tablets USP may be started immediately. An additional method of contraception is not needed if Norgestimate and Ethinyl Estradiol Tablets USP are started immediately.
- If Norgestimate and Ethinyl Estradiol Tablets USP are not started within 5 days after termination of the pregnancy, the patient should use additional non-hormonal contraception (such as condoms and spermicide) for the first seven days of her first cycle pack of Norgestimate and Ethinyl Estradiol Tablets USP.

Second-trimester

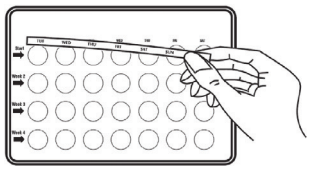
- Do not start until 4 weeks after a second-trimester abortion or miscarriage, due to the increased risk of thromboembolic disease. Start Norgestimate and Ethinyl Estradiol Tablets USP, following the instructions in Table 1 for Day 1 or Sunday start, as desired. If using Sunday start, use additional non-hormonal contraception (such as condoms and spermicide) for the first seven days of the patient's first cycle pack of Norgestimate and Ethinyl Estradiol Tablets USP. [*See Contraindications (4), Warnings and Precautions (5.1), and FDA-Approved Patient Labeling.*]

Starting Norgestimate and Ethinyl Estradiol Tablets USP after Childbirth

- Do not start until 4 weeks after delivery, due to the increased risk of thromboembolic disease. Start contraceptive therapy with Norgestimate and Ethinyl Estradiol Tablets USP following the instructions in Table 1 for women not currently using hormonal contraception.
- Norgestimate and Ethinyl Estradiol Tablets USP are not recommended for use in lactating women [*see Use in Specific Populations (8.3)*].
- If the woman has not yet had a period postpartum, consider the possibility of ovulation and conception occurring prior to use of Norgestimate and Ethinyl Estradiol Tablets USP. [*See Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.1 and 8.3), and FDA-Approved Patient Labeling*].

BEFORE YOU START TAKING YOUR PILLS, SET THE DAY:

- **Day 1 Start:**
  - Pick the day label strip that starts with the first day of your period (this is the day you start bleeding or spotting, even it is almost midnight when the bleeding begins).
  - Place this day label strip on the tablet blister card over the area that has the days of the week (starting with Sunday) printed on the blister.



  - Take the tablets in the direction of the arrows in the picture (from left to right) each week.
  - For Norgestimate and Ethinyl Estradiol Tablets USP, (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg), take the first light blue "active" tablet during the first 24 hours of your period that corresponds with the day of the week the first tablet will be taken.
  - For Norgestimate and Ethinyl Estradiol Tablets USP (0.25 mg/0.035 mg), take the first dark blue "active" tablet during the first 24 hours of your period that corresponds with the day of the week the first tablet will be taken.
- **Sunday Start:**
  - Norgestimate and Ethinyl Estradiol Tablets USP, (0.18 mg/0.035 mg, 0.215 mg/ 0.035 mg and 0.25 mg/0.035 mg) - the first light blue "active" tablet should be taken on the first Sunday after the patient's menstrual period begins. If your period begins on Sunday, start the pack that same day.
  - Norgestimate and Ethinyl Estradiol Tablets USP (0.25 mg/0.035 mg) - the first dark blue "active" tablet should be taken on the first Sunday after the patient's menstrual period begins. If your period begins on Sunday, start the pack that same day.

2.3 Missed Tablets

Table 2: Instructions for Missed Norgestimate and Ethinyl Estradiol Tablets USP

• If one active tablet is missed in Weeks 1, 2, or 3	Take the tablet as soon as possible. Continue taking one tablet a day until the pack is finished.
• If two active tablets are missed in Week 1 or Week 2	Take the two missed tablets as soon as possible and the next two active tablets the next day. Continue taking one tablet a day until the pack is finished. **Additional non-hormonal contraception (such as condoms and spermicide) should be used as back-up if the patient has sex within 7 days after missing tablets.**
• If two active tablets are missed in the third week or three or more active tablets are missed in a row in Weeks 1, 2,or 3	**Day 1 start:** Throw out the rest of the pack and start a new pack that same day. **Sunday start:** Continue taking one tablet a day until Sunday, then throw out the rest of the pack and start a new pack that same day. **Additional non-hormonal contraception (such as condoms and spermicide) should be used as back-up if the patient has sex within 7 days after missing tablets.**

2.4 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*).

2.5 Norgestimate and Ethinyl Estradiol Tablets USP, (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg) Use for Acne

The timing of initiation of dosing with Norgestimate and Ethinyl Estradiol Tablets USP (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg) for acne should follow the guidelines for use of Norgestimate and Ethinyl Estradiol Tablets USP, (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg) as an oral contraceptive. Consult the DOSAGE AND ADMINISTRATION section (2.1) for instructions.

3 DOSAGE FORMS AND STRENGTHS

Norgestimate and Ethinyl Estradiol Tablets USP, (0.25 mg/0.035 mg):

Norgestimate and Ethinyl Estradiol Tablets USP (0.25 mg/0.035 mg) are available in blister cards. Each blister card contains 28 tablets in the following order:

- 21 dark blue unscored round tablets debossed with on one side with "14"; the tablet contains 0.25 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 white round unscored tablets (non-hormonal placebo) debossed on one side with "11"; the tablet contains inert ingredients

Norgestimate and Ethinyl Estradiol Tablets USP (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg):
Norgestimate and Ethinyl Estradiol Tablets USP (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg) are available in blister cards. Each blister card contains 28 tablets in the following order:
- 7 light blue unscored round tablets debossed on one side with "12"; the tablet contains 0.18 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 medium blue unscored round tablets debossed on one side with "13"; the tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 dark blue unscored round tablet debossed on one side with "14"; the tablet contains 0.25 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 white unscored round tablets (non-hormonal placebo) debossed on one side with "11"; the tablet contains inert ingredients

4 CONTRAINDICATIONS

Do not prescribe Norgestimate and Ethinyl Estradiol Tablets USP to women who are known to have the following conditions:
- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 [*see Boxed Warning and Warnings and Precautions (5.1)*]
  - Have deep vein thrombosis or pulmonary embolism, now or in the past [*see Warnings and Precautions (5.1)*]
  - Have inherited or acquired hypercoagulopathies [*see Warnings and Precautions (5.1)*]
  - Have cerebrovascular disease [*see Warnings and Precautions (5.1)*]
  - Have coronary artery disease [*see Warnings and Precautions (5.1)*]
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [*see Warnings and Precautions (5.1)*]
  - Have uncontrolled hypertension [*see Warnings and Precautions (5.3)*]
  - Have diabetes mellitus with vascular disease [*see Warnings and Precautions (5.5)*]
  - Have headaches with focal neurological symptoms or migraine headaches with aura (*see Warnings and Precautions (5.6)*]
    - Women over age 35 with any migraine headaches [*see Warnings and Precautions (5.6)*]
- Liver tumors, benign or malignant, or liver disease [*see Warnings and Precautions (5.2)*]
- Undiagnosed abnormal uterine bleeding [*see Warnings and Precautions (5.7)*]
- Pregnancy, because there is no reason to use COCs during pregnancy [*see Warnings and Precautions (5.8) and Use in Specific Populations (8.1)*]
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past [*see Warnings and Precautions (5.10)*]

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

- Stop Norgestimate and Ethinyl Estradiol Tablets USP if an arterial thrombotic event or venous thromboembolic (VTE) event occurs.
- Stop Norgestimate and Ethinyl Estradiol Tablets USP if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately [*see Adverse Reactions (6.2)*].
- If feasible, stop Norgestimate and Ethinyl Estradiol Tablets USP 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 Norgestimate and Ethinyl Estradiol Tablets USP 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.

5.2 Liver Disease

Impaired Liver Function
Do not use Norgestimate and Ethinyl Estradiol Tablets USP in women with liver disease, such as acute viral hepatitis or severe (decompensated) cirrhosis of liver [*see Contraindications (4)*]. 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 Norgestimate and Ethinyl Estradiol Tablets USP if jaundice develops.

Liver Tumors
Norgestimate and Ethinyl Estradiol Tablets USP are contraindicated in women with benign and malignant liver tumors [*see Contraindications (4)*] Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases/100,000 COC 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 is less than one case per million users.

5.3 High Blood Pressure

Norgestimate and Ethinyl Estradiol Tablets USP are contraindicated in women with uncontrolled hypertension or hypertension with vascular disease [*see Contraindications (4)*]. For women with well-controlled hypertension, monitor blood pressure and stop Norgestimate and Ethinyl Estradiol Tablets USP 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 concentrations of progestin.

5.4 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.

5.5 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who take Norgestimate and Ethinyl Estradiol Tablets USP. 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.

5.6 Headache

If a woman taking Norgestimate and Ethinyl Estradiol Tablets USP develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Norgestimate and Ethinyl Estradiol Tablets USP if indicated.

Consider discontinuation of Norgestimate and Ethinyl Estradiol Tablets USP in the case of increased frequency or severity of migraines during COC use (which may be prodromal of a cerebrovascular event).

5.7 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 clinical trials of Norgestimate and Ethinyl Estradiol Tablets USP, the frequency and duration of breakthrough bleeding and/or spotting was assessed in 1,647 patients (21,275 evaluable cycles) and 4,826 patients (35,546 evaluable cycles), respectively. A total of 100 (7.5%) women discontinued Norgestimate and Ethinyl Estradiol Tablets USP, (0.25 mg/0.035 mg) and 231 (4.8%) women discontinued Norgestimate and Ethinyl Estradiol Tablets USP, (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg), at least in part, due to bleeding or spotting. Based on data from the clinical trials, 14-34% of women using Norgestimate and Ethinyl Estradiol Tablets USP, (0.25 mg/0.035 mg) experienced unscheduled bleeding per cycle in the first year; for Norgestimate and Ethinyl Estradiol Tablets USP, (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg), the respective numbers were 13-38%. The percent of women who experienced breakthrough/unscheduled bleeding tended to decrease over time

Amenorrhea and Oligomenorrhea
Women who use Norgestimate and Ethinyl Estradiol Tablets USP may experience amenorrhea. 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.

5.8 COC Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb reduction defects are concerned, when oral contraceptives are taken inadvertently during early pregnancy. Discontinue Norgestimate and Ethinyl Estradiol Tablets USP use if pregnancy is confirmed.

Administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy [*see Use in Specific Populations (8.1)*].

5.9 Depression

Carefully observe women with a history of depression and discontinue Norgestimate and Ethinyl Estradiol Tablets USP if depression recurs to a serious degree.

5.10 Carcinoma of Breast and Cervix

- Norgestimate and Ethinyl Estradiol Tablets USP are contraindicated in women who currently have or have had breast cancer because breast cancer may be hormonally sensitive [*see Contraindications (4)*].

  There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.
- 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.

5.11 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.

5.12 Monitoring
A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.13 Hereditary Angioedema
In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

5.14 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 Norgestimate and Ethinyl Estradiol Tablets USP.

6 ADVERSE REACTIONS
The following serious adverse reactions with the use of COCs are discussed elsewhere in labeling:
- Serious cardiovascular events and stroke [*see Boxed Warning and Warnings and Precautions (5.1)*]
- Vascular events [*see Warnings and Precautions (5.1)*]
- Liver disease [*see Warnings and Precautions (5.2)*]

Adverse reactions commonly reported by COC users are
- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trial 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.

Norgestimate and Ethinyl Estradiol Tablets USP, (0.25 mg/0.035 mg)
The safety of Norgestimate and Ethinyl Estradiol Tablets USP, (0.25 mg/0.035 mg) was evaluated in 1,647 healthy women of child-bearing potential who participated in 3 clinical trials and received at least 1 dose of Norgestimate and Ethinyl Estradiol Tablets USP, (0.25 mg/0.035 mg) for contraception. Two trials were randomized active-controlled trials and 1 was an uncontrolled open-label trial. In all 3 trials, subjects were followed for up to 24 cycles.

Common Adverse Reactions (≥2% of subjects): The most common adverse reactions reported by at least 2% of the 1,647 women were the following in order of decreasing incidence: headache/migraine (32.9%), abdominal/gastrointestinal pain (7.8%), vaginal infection (8.4%), genital discharge (6.8%), breast issues (including breast pain, discharge, and enlargement) (6.3%), mood disorders (including depression and mood altered) (5.0%), flatulence (3.2%), nervousness (2.9%), and rash (2.6%).

Adverse Reactions Leading to Study Discontinuation: Over the three trials, between 11 to 21% of subjects discontinued the trial due to an adverse reaction. The most common adverse reactions (≥1%) leading and discontinuation were: metrorrhagia (6.9%), nausea/vomiting (5.0%), headache (4.1%), mood disorders (including depression and mood altered) (2.4%), premenstrual syndrome (1.7%), hypertension (1.4%), breast pain (1.4%), nervousness (1.3%), amenorrhea (1.1%), dysmenorrhea (1.1%), Weight increased (1.1%), and flatulence (1.1%).

Serious Adverse Reactions: breast cancer (1 subject), mood disorders including depression, irritability, and mood swings (1 subject), myocardial infarction (1 subject), and venous thromboembolic events including pulmonary embolism (1 subject) and deep vein thrombosis (DVT) (1 subject).

Norgestimate and Ethinyl Estradiol Tablets USP, (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg)
The safety of Norgestimate and Ethinyl Estradiol Tablets USP, (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg) was evaluated in 4,826 healthy women of child-bearing potential who participated in 6 clinical trials and received at least 1 dose of Norgestimate and Ethinyl Estradiol Tablets USP, (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg) for contraception. Two trials were randomized active-controlled trials and 4 were uncontrolled open-label trials. In 3 trials, subjects were followed for up to 24 cycles; in 2 trials, subjects were followed for up to 12 cycles; and in 1 trial, subjects were followed for up to 6 cycles.

Common Adverse Reactions (≥2% of subjects): The most common adverse reactions reported by at least 2% of the 4,826 women were the following in order of decreasing incidence: headache/migraine (33.6%), breast issues (including breast pain, enlargement, and discharge) (8.0%), vaginal infection (7.1%), abdominal/gastrointestinal pain (5.6%), mood disorders (including mood alteration and depression)(3.8%), genital discharge (3.2%), and changes in weight (including weight fluctuation, increased or decreased) (2.5%).

Adverse Reactions Leading to Study Discontinuation: Over the trials, between 9 to 27% of subjects discontinued the trial due to an adverse reaction. The most common adverse reactions (≥1%) leading and discontinuation were: metrorrhagia (4.3%), nausea/vomiting (2.8%), headache/migraine (2.4%), mood disorders (including depression and mood altered) (1.1%), and weight increased (1.1%).

Serious Adverse Reactions: breast cancer (1 subject), carcinoma of the cervix in situ (1 subject), hypertension (1 subject), and migraine (2 subjects).

6.2 Postmarketing Experience
The following additional adverse drug reactions have been reported from worldwide postmarketing experience with norgestimate/ethinyl estradiol. 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.

Infections and Infestations: Urinary tract infection;

Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps): Breast cancer, benign breast neoplasm, hepatic adenoma, focal nodular hyperplasia, breast cyst;

Immune System Disorders: Hypersensitivity;

Metabolism and Nutrition Disorders: Dyslipidemia;

Psychiatric Disorders: Anxiety, insomnia;

Nervous System Disorders: Syncope, convulsion, paresthesia, dizziness;

Eye Disorders: Visual impairment, dry eye, contact lens intolerance;

Ear and Labyrinth Disorders: Vertigo;

Cardiac Disorders: Tachycardia, palpitations;

Vascular Events: Deep vein thrombosis, pulmonary embolism, retinal vascular thrombosis, hot flush;

Arterial Events: Arterial thromboembolism, myocardial infarction, cerebrovascular accident;

Respiratory Thoracic and Mediastinal Disorders: Dyspnea;

Gastrointestinal Disorders: Pancreatitis, abdominal distension, diarrhea, constipation;

Hepatobiliary Disorders: Hepatitis;

Skin and Subcutaneous Tissue Disorders: Angioedema, erythema nodosum, hirsutism, night sweats, hyperhidrosis, photosensitivity reaction, urticaria, pruritus, acne;

Musculoskeletal, Connective Tissue, and Bone Disorders: Muscle spasms, pain in extremity, myalgia, back pain;

Reproductive System and Breast Disorders: Ovarian cyst, suppressed lactation, vulvovaginal dryness;

General Disorders and Administration Site Conditions: Chest pain, asthenic conditions.

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

No drug-drug interaction studies were conducted with Norgestimate and Ethinyl Estradiol Tablets USP.

7.1 Effects of Other Drugs on Combined Oral Contraceptives
Substances decreasing the plasma concentrations 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 ethinyl estradiol (EE) increase AUC values for EE by approximately 20-25%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole, voriconazole, 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 estrogen and/or progestin have been noted in some cases of co-administration with 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., boceprevir and telaprevir]) or with non-nucleoside reverse transcriptase inhibitors (decrease [e.g., nevirapine] or increase [e.g., etravirine]).

7.2 Effects of Combined Oral Contraceptives on Other Drugs
- COCs containing EE may inhibit the metabolism of other compounds (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 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 the serum concentration of thyroid-binding globulin increases with use of COCs.

7.3 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.

8 USE IN SPECIFIC POPULATIONS
8.1 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 non-genital birth defects (including cardiac anomalies and limb reduction defects) following exposure to low-dose COCs prior to conception or during early pregnancy.

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.

8.3 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.

8.4 Pediatric Use
Safety and efficacy of Norgestimate and Ethinyl Estradiol Tablets USP have been established in women of reproductive age. Efficacy is expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

There was no significant difference between Norgestimate and Ethinyl Estradiol Tablets USP (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg) and placebo in mean change in total lumbar spine (L1-L4) and total hip bone mineral density between baseline and Cycle 13 in 123 adolescent females with anorexia nervosa in a double-blind, placebo-controlled, multicenter, one-year treatment duration clinical trial for the Intent To Treat (ITT) population.

8.5 Geriatric Use
Norgestimate and Ethinyl Estradiol Tablets USP have not been studied in postmenopausal women and are not indicated in this population.

8.6 Hepatic Impairment
The pharmacokinetics of Norgestimate and Ethinyl Estradiol Tablets USP have not been studied in subjects with hepatic impairment. However, steroid hormones may be poorly metabolized in patients with hepatic impairment. 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. [*See Contraindications (4) and Warnings and Precautions (5.2)*].

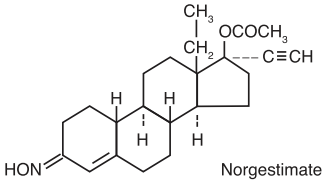
8.7 Renal Impairment
The pharmacokinetics of Norgestimate and Ethinyl Estradiol Tablets USP have not been studied in women with renal impairment.

10 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.

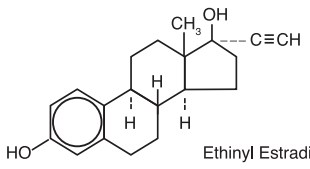
11 DESCRIPTION
Each of the following products is a combination oral contraceptive containing the progestational compound norgestimate and the estrogenic compound ethinyl estradiol. Norgestimate is designated as (18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime,(17α)-(+)-) and ethinyl estradiol is designated as (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol).

Norgestimate and Ethinyl Estradiol Tablets USP, (0.25 mg/0.035 mg)
- Each active dark blue tablet contains 0.25 mg of norgestimate and 0.035 mg of ethinyl estradiol. Inactive ingredients include colloidal silicon dioxide, FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate and pregelatinized corn starch.
- Each white placebo tablet containing only inert ingredients, as follows: lactose, magnesium stearate, microcrystalline cellulose and pregelatinized corn starch.

Norgestimate and Ethinyl Estradiol Tablets, USP (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg)
- Each active light blue tablet contains 0.18 mg of norgestimate and 0.035 mg of ethinyl estradiol. Inactive ingredients include colloidal silicon dioxide, FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate and pregelatinized corn starch.
- Each active medium blue tablet contains 0.215 mg of norgestimate and 0.035mg of ethinyl estradiol. Inactive ingredients include colloidal silicon dioxide, FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate and pregelatinized corn starch.
- Each active dark blue tablet contains 0.25 mg of norgestimate and 0.035 mg of ethinyl estradiol. Inactive ingredients include colloidal silicon dioxide, FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate and pregelatinized corn starch.
- Each white placebo tablet contains only inert ingredients, as follows: lactose, magnesium stearate, microcrystalline cellulose and pregelatinized corn starch.



Norgestimate



Ethinyl Estradiol

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
- Oral Contraception
  COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.
- Acne
  Acne is a skin condition with a multifactorial etiology, including androgen stimulation of sebum production. While the combination of ethinyl estradioland norgestimate increases sex homone-binding globulin (SHBG) and decreases free testosterone, the relationship between these changes and a decrease in the severity of facial acne in otherwise healthy women with this skin condition has not been established.

12.2 Pharmacodynamics
No specific pharmacodynamic studies were conducted with Norgestimate and Ethinyl Estradiol Tablets USP.

12.3 Pharmacokinetics
Absorption
Norgestimate (NGM) and EE are rapidly absorbed following oral administration. NGM is rapidly and completely metabolized by first-pass (intestinal and/or hepatic) mechanisms to norelgestromin (NGMN) and norgestrel (NG), which are the major active metabolites of norgestimate.

Peak serum concentrations of NGMN and EE are generally reached by 2 hours after administration of Norgestimate and Ethinyl Estradiol Tablets USP. Accumulation following multiple dosing of the 250 mcg NGM/35 mcg EE dose is approximately 2-fold for NGMN and EE compared with single dose administration. The pharmacokinetics of NGMN is dose-proportional following NGM doses of 180 mcg to 250 mcg. Steady-state concentration of EE is achieved by Day 7 of each dosing cycle. Steady-state concentrations of NGMN and NG are achieved by Day 21. Non-linear accumulation (approximately 8-fold) of NG is observed as a result of high-affinity binding to SHBG, which limits its biological activity (Table 3).

Table 3: Summary of NGMN, NG and EE pharmacokinetic parameters

Mean (SD) Pharmacokinetic Parameters of Norgestimate and Ethinyl Estradiol Tablets USP, (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg) During a Three-Cycle Study						
Analyte	Cycle	Day	C_{max}	t_{max}(h)	AUC_{0-24h}	$t_{1/2}$(h)
NGMN	3	7	1.80 (0.46)	1.42 (0.73)	15.0 (3.88)	NC
		14	2.12 (0.56)	1.21 (0.26)	16.1 (4.97)	NC
		21	2.66 (0.47)	1.29 (0.26)	21.4 (3.46)	22.3 (6.54)
NG	3	7	1.94 (0.82)	3.15 (4.05)	34.8 (16.5)	NC
		14	3.00 (1.04)	2.21 (2.03)	55.2 (23.5)	NC
		21	3.66 (1.5)	2.58 (2.97)	69.3 (23.8)	40.2 (15.4)
EE	3	7	124 (39.5)	1.27 (0.26)	1130 (420)	NC
		14	128 (38.4)	1.32 (0.25)	1130 (324)	NC
		21	126 (34.7)	1.31 (0.56)	1090 (359)	15.9 (4.39)
Mean (SD) Pharmacokinetic Parameters of Norgestimate and Ethinyl Estradiol Tablets USP, (0.25 mg/0.035 mg) During a Three-Cycle Study						
Analyte	Cycle	Day	C_{max}	t_{max}(h)	AUC_{0-24h}	$t_{1/2}$(h)
NGMN	1	1	1.78 (0.397)	1.19 (0.250)	9.90 (3.25)	18.4 (5.91)
	3	21	2.19 (0.655)	1.43 (0.680)	18.1 (5.53)	24.9 (9.04)
NG	1	1	0.649 (0.49)	1.42 (0.69)	6.22 (2.46)	37.8 (14.0)
	3	21	2.65 (1.11)	1.67 (1.32)	48.2 (20.5)	45.0 (20.4)
EE	1	1	92.2 (24.5)	1.2 (0.26)	629 (138)	10.1 (1.90)
	3	21	147 (41.5)	1.13 (0.23)	1210 (294)	15.0 (2.36)
C_{max} = peak serum concentration, t_{max} = time to reach peak serum concentration, AUC_{0-24h} = area under serum concentration vs time curve from 0 to 24 hours, $t_{1/2}$ = elimination half-life, NC = not calculated.						
NGMN and NG: C_{max} = ng/mL, AUC_{0-24h} = h·ng/mL						
EE: C_{max} =pg/mL, AUC_{0-24h} = h·pg/mL						

Food Effect
The effect of food on the pharmacokinetics of Norgestimate and Ethinyl Estradiol Tablets USP has not been studied.

Distribution
NGMN and NG are highly bound (>97%) to serum proteins. NGMN is bound to albumin and not to SHBG, while NG is bound primarily to SHBG. EE is extensively bound (>97%) to serum albumin and induces an increase in the serum concentrations of SHBG.

Metabolism
NGM is extensively metabolized by first-pass mechanisms in the gastrointestinal tract and/or liver. NGM's primary active metabolite is NGMN. Subsequent hepatic metabolism of NGMN occurs and metabolites include NG, which is also active, and various hydroxylated and conjugated metabolites. Although NGMN and its metabolites inhibit a variety of P450 enzymes in human liver microsomes, under the recommended dosing regimen, the *in vivo* concentrations of NGMN and its metabolites, even at the peak serum levels, are relatively low compared to the inhibitory constant (K_i), EE is also metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.

Excretion
The metabolites of NGMN and EE are eliminated by renal and fecal pathways. Following administration of ^{14}C-norgestimate, 47% (45-49%) and 37% (16-49%) of the administered

radioactivity was eliminated in the urine and feces, respectively. Unchanged NGM was not detected in the urine. In addition to 17-deacetyl norgestimate, a number of metabolites of NGM have been identified in human urine following administration of radiolabeled NGM. These include 18, 19-Dinor-17-pregn-4-en-20-yn-3-one, 17-hydroxy-3-ethyl(17α)-(-):18, 19-Dinor-5ß-17-pregnan-20-yn,3α,17ß-dihydroxy-3-ethyl (17α), various hydroxylated metabolites and conjugates of these metabolites.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[*See Warnings and Precautions (5.2, 5.10) and Use in Specific Populations (8.1)*].

14 CLINICAL STUDIES

14.1 Contraception

In three US clinical trials with Norgestimate and Ethinyl Estradiol Tablets USP, (0.25 mg/0.035 mg), 1,651 women aged 18 to 38 years were studied for up to 24 cycles, providing a total of 24,272 cycles of exposure. The racial demographic was about 73-86% Caucasian, 8-13% African-American, 6-14% Hispanic with the remainder Asian or Other (≤1%). There were no exclusions on the basis of weight; the weight range for women treated was 82-303 lbs, with a mean weight of about 135 lbs. The pregnancy rate was approximately 1 pregnancy per 100 women-years.

In four clinical trials with Norgestimate and Ethinyl Estradiol Tablets USP, (0.18 mg/0.035 mg, 0.25 mg/0.035 mg and 0.25 mg/0.035 mg), 4,756 women aged 15 to 41 years were studied for 24 cycles, providing a total of 45,244 cycles of exposure. The racial demographic was about 87-90% Caucasian, 6-10% African-American, with the remainder Asian (<1%) or Other (2-5%). There were no exclusions on the basis of weight; the weight range for women treated was 80-310 lbs, with a mean weight of about 132 lbs. The pregnancy rate was approximately 1 pregnancy per 100 women-years.

14.2 Acne

Norgestimate and Ethinyl Estradiol Tablets USP, (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg) was evaluated for the treatment of acne vulgaris in two randomized, double-blind, placebo-controlled, multicenter, six-(28 day) cycle studies. Two hundred twenty-one patients received Norgestimate and Ethinyl Estradiol Tablets USP, (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg) and 234 patients received placebo. Mean age at enrollment for both groups was 28 years. At the end of 6 months, the mean total lesion count changed from 55 to 31 (42% reduction) in patients treated with Norgestimate and Ethinyl Estradiol Tablets USP, (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg) and from 54 to 38 (27% reduction) in patients similarly treated with placebo. Table 4 summarizes the changes in lesion count for each type of lesion. Based on the investigator's global assessment conducted at the final visit, patients treated with Norgestimate and Ethinyl Estradiol Tablets USP (0.18 mg/0.035 mg/0.215 mg/0.035 mg and 0.25 mg/0.035 mg) showed a statistically significant improvement in total lesions compared to those treated with placebo.

Table 4: Acne Vulgaris Indication. Combined Results: Two Multicenter, Placebo-Controlled Trials. Observed Means at Six Months (LOCF) and at Baseline. Intent-to-Treat Population.

Norgestimate and Ethinyl Estradiol Tablets USP, (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg) (N=221)			Placebo (N=234)		Difference in Counts between Norgestimate and Ethinyl Estradiol Tablets USP, (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg) and Placebo at 6 Months
# of Lesions	Counts	% Reduction	Counts	% Reduction	
INFLAMMATORY LESIONS					
Baseline Mean	19		19		
Six Month Mean	10	48%	13	30%	3 (95% CI: -1.2, 5.1)
NON-INFLAMMATORY LESIONS					
Baseline Mean	36		35		
Six Month Mean	22	34%	25	21%	3 (95% CI: -0.2, 7.8)
TOTAL LESIONS					
Baseline Mean	55		54		
Six Month Mean	31	42%	38	27%	7 (95% CI: 2.0, 11.9)

* LOCF: Last Observation Carried Forward

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Norgestimate and Ethinyl Estradiol Tablets, USP, (0.25 mg/0.035 mg)

Norgestimate and Ethinyl Estradiol Tablets USP, (0.25 mg/0.035 mg) are available in a blister card: (NDC 17478-260-28).

Each blister card (28 tablets) contains in the following order:

- 21 dark blue unscored round tablets debossed with on one side with "14"; the tablet contains 0.25 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 white round unscored tablets (non-hormonal placebo) debossed on one side with "11"; the tablet contains inert ingredients

Norgestimate and Ethinyl Estradiol Tablets USP, (0.25 mg/0.035mg) are packaged in a carton (NDC 17478-260-06) containing 6 blister cards.

Norgestimate and Ethinyl Estradiol Tablets USP, (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg)

Norgestimate and Ethinyl Estradiol Tablets USP, (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg) are available in a blister card(NDC 17478-261-28).

Each blister card (28 tablets) contains in the following order:

- 7 light blue unscored round tablets debossed on one side with "12"; the tablet contains 0.18 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 medium blue unscored round tablets debossed on one side with "13"; the tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 dark blue unscored round tablet debossed on one side with "14"; the tablet contains 0.25 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 white unscored round tablets (non-hormonal placebo) debossed on one side with "11"; the tablet contains inert ingredients

Norgestimate and Ethinyl Estradiol Tablets USP, (0.18 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg) are packaged in a carton containing 6 blister cards: (NDC 17478-261-06).

Keep out of reach of children.

16.2 Storage Conditions

- Store at 20° to 25°C (68° to77°F), excursions permitted to 15° to 30°C (59 to 86°F).
- Protect from light.

17 PATIENT COUNSELING INFORMATION

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 [*see Warnings and Precautions (5.1)*].
- Norgestimate and Ethinyl Estradiol Tablets USP do not protect against HIV infection (AIDS) and other sexually transmitted infections.
- Norgestimate and Ethinyl Estradiol Tablets USP are not to be used during pregnancy; if pregnancy occurs during use of Norgestimate and Ethinyl Estradiol Tablets USP, instruct the patient to stop further use [*see Warnings and Precautions (5.8)*].
- Take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event tablets are missed [*see Dosage and Administration (2.2)*].
- Use a back-up or alternative method of contraception when enzyme inducers are used with Norgestimate and Ethinyl Estradiol Tablets USP [*see Drug Interactions (7.1)*].
- COCs may reduce breast milk production; this is less likely to occur if breastfeeding is well established [*see Use in Specific Populations (8.3)*].
- 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 [*see Dosage and Administration (2.2)*].
- 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 [*see Warnings and Precautions (5.7)*].

AKORN
Manufactured for:
Akorn, Inc.
Lake Forest, IL 60045

Product Made in Poland

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