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Letter of Testimony in Support of House Bill 2523

Members of the House Judiciary Committee,

I am a Roman Catholic. I am a husband, a father of six children, and a grandfather of two children. I have Bachelor of Arts Degrees in Music Performance, Biology, and Chemistry from Washburn University and a Bachelor of Science Degree in Pharmacy from the University of Kansas School of Pharmacy. I have been a licensed Registered Pharmacist in Kansas since 1997. I have always worked in the retail pharmacy setting: Medical Arts Pharmacy in Topeka 1997-1998, Walgreens Pharmacy in North Topeka 1998-1999, and St Marys Pharmacy in St Marys, KS 1999-present. My wife, also a pharmacist, and I additionally became small business owners when we purchased the pharmacy in St Marys in 2004. I have also served a member of the Kansas Medicaid Drug Utilization Review Board for the last two years.

When I graduated as a pharmacist I took an oath, The Oath of a Pharmacist. The oath reads as follows... At this time, I vow to devote my professional life to the service of all humankind through the profession of pharmacy. I will consider the welfare of humanity and relief of human suffering my primary concerns. I will apply my knowledge, experience, and skills to the best of my ability to assure optimal drug therapy outcomes for the patients I serve. I will keep abreast of developments and maintain professional competency in my profession of pharmacy. I will maintain the highest principles of moral, ethical, and legal conduct. I will embrace and advocate change in the profession of pharmacy that improves patient care. I take these vows voluntarily with the full realization of the responsibility with which I am entrusted by the public...

I take those vows seriously. I have heard some people state openly that when you become a pharmacist you must check your religion at the door. Meaning regardless of your beliefs you are required to provide willingly and completely all possible services to or for patients including emergency contraception such as Plan B and Ella and or other contraceptive products. I am certain other medical professionals experience similar pressure to provide abortive procedures without regard to their personal convictions. As a practicing Roman Catholic such a separation between my professional life and my religious convictions is not possible. I don't have the capacity to check my conscience at the door when I clock in to work. I believe as a tenant of my faith that all life is sacred, and additionally that abortion is an intrinsic evil. In my store I have sought to practice both my profession and live my faith.

It is important for the purposes of this testimony to briefly describe the mechanisms of action by which contraceptive and emergency contraceptive products exhibit their effects.

The following drug information was copied from Lexicomp, a drug information resource I utilize in my day to day practice, with the exception of the descriptions (preventative) and (abortive). I added these to assist the committee's understanding of which mechanisms might act to prevent the fertilization of an egg by a sperm, and which mechanisms result in the aborting of a new life, a fertilized viable egg. The drug information found in Lexicomp is the same as the drug information produced by the drug manufacturers.

Plan B (emergency contraception): Pregnancy may be prevented through several mechanisms: Thickening of cervical mucus, which inhibits sperm passage through the uterus and sperm survival (preventative); inhibition of ovulation, from a negative feedback mechanism on the hypothalamus, leading to reduced secretion of follicle stimulating hormone and luteinizing hormone (preventative); and inhibition of implantation (abortive).

Ella (emergency contraception): The exact mechanism of action of ulipristal (Ella) is unknown, but may involve inhibition or delay of ovulation or inhibition of follicular growth or rupture (preventative); alteration to the endometrium that may affect implantation also may contribute to efficacy (abortive).

All other Oral Contraceptives (may be considered regular birth control): Combination oral contraceptives (containing estrogen and progestin or their derivations) inhibit ovulation via a negative feedback mechanism on the hypothalamus, which alters the normal pattern of gonadotropin secretion of a follicle-stimulating hormone and luteinizing hormone by the anterior pituitary (preventative); alterations of the genital tract, including changes in the cervical mucus, rendering it unfavorable for sperm penetration even if ovulation occurs (preventative); changes in the endometrium may also occur, producing an unfavorable environment for nidation or implantation(abortive); Combination hormonal contraceptive drugs may alter the tubal transport of the ova through the fallopian tubes (preventative); Progestational agents may also alter sperm fertility (preventative).

It is also important to note that the Pharmacy Practice Act provides little to no protection for the refusal to fill or refill a prescription based upon religious liberty and freedom of conscience. The statute (65-1637) states after describing how prescriptions are to be filled or refilled... “Nothing contained in this section shall be construed as preventing a pharmacist from refusing to fill or refill any prescription if in the pharmacist's professional judgment and discretion such pharmacist is of the opinion that it should not be filled or refilled.” The statute implies a pharmacist may refuse to fill a prescription according to their professional judgment, for example perhaps refusing to fill due to a potentially dangerous drug-drug interaction or disease/condition-drug interaction; and discretion, perhaps the patient is a narcotic drug seeker trying to utilize multiple pharmacies. The statute does not overtly state that a pharmacist may refuse to fill based upon religious liberty and freedom of conscience.

My confession to this committee is that I have only been partially successful in living my faith life and practicing my profession. At this time in my business I have chosen not to carry emergency contraceptives, that is my line in the sand so far, and I feel like I am on very thin ice. I currently stock and dispense oral contraceptives in my pharmacy. It is clear all contraceptive products have the potential to be abortifacients. I would like to remove all contraception products from my business, but the truth is I have not done so out of fear. I fear being sued. There is no protection for the freedom of conscience under the current statute. It is not my desire to foist my religion on anybody, however I should be free to exercise my conscience without fear of reprisal. I urge the committee to forward House Bill 2523 and amend KSA 65-433.

Sincerely,

Daniel H. Sutherland RPh

Levonorgestrel  
(Lexi-Drugs)  
Pronunciation

(LEE voh nor jes trel)  
Brand Names: U.S.

Mirena®; Next Choice™; Plan B® One Step  
Brand Names: Canada

Mirena®; Plan B®  
Pharmacologic Category

Contraceptive; Progestin  
Dosing: Adult

Females:

Long-term prevention of pregnancy, treatment of heavy menstrual bleeding: Intrauterine device (Mirena®): To be inserted into uterine cavity; should be inserted within 7 days of onset of menstruation or immediately after 1st trimester abortion. Releases 20 mcg levonorgestrel/day over 5 years. May be removed and replaced with a new unit at anytime during menstrual cycle. Do not leave any one system in place for >5 years.

Emergency contraception: Oral: May be used at any time during menstrual cycle:

Next Choice™: One 0.75 mg tablet as soon as possible within 72 hours of unprotected sexual intercourse; a second 0.75 mg tablet should be taken 12 hours after the first dose

Plan B® One-Step: One 1.5 mg tablet as soon as possible within 72 hours of unprotected sexual intercourse  
Dosing: Geriatric

Not indicated for use in postmenopausal women.  
Dosing: Renal Impairment

Safety and efficacy have not been established.  
Dosing: Hepatic Impairment

Safety and efficacy have not been established; use of the intrauterine device is contraindicated with active hepatic disease or hepatic tumor.  
Use: Labeled Indications

Intrauterine device (IUD): Prevention of pregnancy; treatment of heavy menstrual bleeding in women who also choose to use an IUD for contraception

Oral: Emergency contraception following unprotected intercourse or possible contraceptive failure

Plan B® One-Step is approved for OTC use by women ≥17 years of age and available by prescription only for women <17 years of age. Next Choice™ (generic of the original Plan-B® 2-dose regimen) is also approved for OTC use by women ≥17 years of age and by prescription only for women <17 years of age.  
Clinical Practice Guidelines

CDC, "U.S. Medical Eligibility Criteria for Contraceptive Use, 2010," MMWR, May 2010  
Administration: Oral

Oral (Plan B® One Step): Consider repeating the dose if vomiting occurs within 2 hours. If severe vomiting occurs, may consider administering the oral tablets vaginally (ACOG, 2010).

Administration: Other

Intrauterine device: Inserted in the uterine cavity, to a depth of 6-10 cm, with the provided insertion device; should not be forced into the uterus

Oral tablets: If severe vomiting occurs, may consider administering the oral tablets vaginally (ACOG, 2010).

Storage

Store at room temperature of 20°C to 25°C (68°F to 77°F).

Prescribing and Access Restrictions

Plan B® One-Step will be limited to pharmacies or healthcare clinics with a valid license to distribute prescription products. Because there will be one package for both OTC and prescription use, pharmacies are required to keep the product behind the counter.

Contraindications

Hypersensitivity to levonorgestrel or any component of the formulation; pregnancy

Additional product-specific contraindications:

Intrauterine device: Congenital or acquired uterine anomaly, acute pelvic inflammatory disease, history of pelvic inflammatory disease (unless there has been a subsequent intrauterine pregnancy), postpartum endometritis or infected abortion within past 3 months, known or suspected uterine or cervical neoplasia, unresolved/abnormal Pap smear, untreated acute cervicitis or vaginitis, conditions which increase susceptibility to pelvic infections, unremoved IUD, undiagnosed abnormal uterine bleeding, active hepatic disease or hepatic tumors, current or history of known or suspected carcinoma of the breast

Oral: It is not known if the same contraindications associated with long term progestin only contraceptives apply to the use of levonorgestrel and the emergency 2-dose regimen. A history of ectopic pregnancy is not a contraindication to use in emergency contraception.

Warnings/Precautions

Concerns related to adverse effects:

- Abdominal pain: Patients taking progestin-only contraceptives and presenting with lower abdominal pain should be evaluated for follicular atresia and ectopic pregnancy.
- Bleeding irregularities: Menstrual bleeding patterns may be altered with use of the intrauterine device; the possibility of pregnancy should be considered if menstruation does not occur within 6 weeks of the previous menstrual period. If bleeding irregularities continue with prolonged use, appropriate diagnostic measures should be taken to rule out endometrial pathology. An increase in menstrual bleeding may indicate a partial or complete expulsion of the IUD. If expulsion occurs, device may be replaced within 7 days once pregnancy is ruled out. When using the oral tablet, spotting may occur following use; the possibility of pregnancy should be considered if menstruation is delayed for >7 days of the expected menstrual period.
- Bradycardia/syncope: Bradycardia or syncope may occur during insertion or removal of the intrauterine device.
- Breast cancer: The use of combination hormonal contraceptives has been associated with a slight increase in the frequency of breast cancer, however, studies are not consistent. Data is

insufficient to determine if progestin only contraceptives also increase this risk. Use of the intrauterine device is contraindicated in patients who have or who have had breast cancer.

- Carbohydrate intolerance: May have adverse effects on glucose tolerance; use caution in women with diabetes.

- Ectopic pregnancy: Use caution in patients with previous ectopic pregnancy. Women with history of ectopic pregnancy were excluded from clinical trials; women with previous ectopic pregnancy, tubal surgery or pelvic infection may be at increased risk ectopic pregnancy. The possibility of ectopic pregnancy should be considered in patients with abdominal pain or vaginal bleeding in women with prior amenorrhea.

Disease-related concerns:

- Renal impairment: Safety and efficacy have not been established for use in renal impairment.

Concurrent drug therapy issues:

- Hepatic enzyme-inducing medications: Patients receiving hepatic enzyme-inducing medications should be evaluated for an alternative method of contraception.

Special populations:

- Pediatrics: Not for use prior to menarche.

- Postmenopausal women: Not indicated for use in postmenopausal women.

- Smokers: The risk of cardiovascular side effects increases in women using estrogen containing combined hormonal contraceptives and who smoke cigarettes, especially those who are >35 years of age. This risk relative to progestin-only contraceptives has not been established. Women who take contraceptives should be advised not to smoke.

Dosage form specific issues:

- Intrauterine device: Increased incidence of group A streptococcal sepsis and pelvic inflammatory disease (may be asymptomatic). The highest risk of pelvic inflammatory disease is within 20 days of insertion; risk is increased with multiple sexual partners. May perforate uterus or cervix; risk of perforation is increased in lactating women. Pregnancy may result if perforation occurs; delayed detection of perforation may result in migration of IUD outside of uterine cavity. Partial penetration or embedment in the myometrium may decrease effectiveness and lead to difficult removal. Use caution in patients with coagulopathy or receiving anticoagulants. Use caution in patients with congenital heart disease or other heart conditions which may increase the risk of infective endocarditis during insertion of the device (prophylactic antibiotics may be required at time of insertion).

- Oral tablet: Not intended to be used for routine contraception and will not terminate an existing pregnancy.

Other warnings/precautions:

- Appropriate use: Intrauterine device: Insertion should be done by a trained health care provider. The device should be removed for the following reasons: Bleeding which causes anemia; if the patient or her partner become HIV positive or acquire a sexually-transmitted disease; pelvic infection, endometritis, symptomatic genital actinomyces; intractable pelvic pain, pain during intercourse; endometrial or cervical cancer; uterine or cervical perforation; pregnancy. Embedded devices should also be removed. Use with caution or consider removal of the intrauterine device

if any of the following conditions occur for the first time during therapy: Migraine, severe headache, jaundice, marked increase in blood pressure, severe arterial disease (eg, stroke, MI). Use is contraindicated in patients with vaginitis or cervicitis. Postpone insertion until after treatment for infection is complete and cause of the cervicitis is proven not to be due to gonorrhea or chlamydia. Not effective for emergency contraception.

- Fertility: Oral tablet: Barrier contraception is recommended immediately following emergency contraception and throughout the same menstrual cycle; efficacy of hormonal contraception may be decreased.

- HIV infection protection: Hormonal contraceptives do not protect against HIV infection or other sexually-transmitted diseases.

#### Pregnancy Considerations

Epidemiologic studies have not shown an increased risk of birth defects when used prior to pregnancy or inadvertently during early pregnancy, although rare reports of congenital anomalies have been reported. In doses larger than those used for oral contraception, progestins have been reported to increase the risk of masculinization of female genitalia.

Intrauterine device: Pregnancy should be ruled out prior to insertion. Women who become pregnant with an IUD in place risk septic abortion (septic shock and death may occur). Removal of the device is recommended, however, removal or manipulation of IUD may result in pregnancy loss. In addition, miscarriage, premature labor, and premature delivery may occur if pregnancy is continued with IUD in place. Following pregnancy, insertion of the device should not take place until 6 weeks postpartum or until involution of the uterus is complete. Consider waiting until 12 weeks postpartum if involution is substantially delayed. The device may be inserted immediately following a first trimester abortion. Following removal of the device, ~80% of women who wished to conceive became pregnant within 12 months.

Oral tablet: A rapid return of fertility is expected following use for emergency contraception; routine contraceptive measures should be initiated or continued following use to ensure ongoing prevention of pregnancy. Barrier contraception is recommended immediately following emergency contraception. Short-term contraception (eg, oral hormonal contraceptive pills, patches, rings) may be started with barrier contraception or after the next menstrual period. Long term contraception (eg, IUD, depot medroxyprogesterone, progestin implant) should be started after the next menstrual period.

#### Lactation

Enters breast milk/use caution  
Breast-Feeding Considerations

Levonorgestrel is found in breast milk. Following long-term use of oral levonorgestrel, infant serum levels range from 1% to 6% of the maternal level; detectable levels may be found in nursing infants. Isolated cases of decreased milk production have been reported. Risk of perforation with IUD is increased in lactating women. Following pregnancy, insertion of the device should not take place until 6 weeks postpartum or until involution of the uterus is complete. Consider waiting until 12 weeks postpartum if involution is substantially delayed. Women who are breast-feeding may use levonorgestrel for emergency contraception.

#### Adverse Reactions

Intrauterine device:

>5%:

Central nervous system: Headache/migraine (8%), depression (6%)

Dermatologic: Acne (7%)

Endocrine & metabolic: Amenorrhea (24%; 20% at 1 year), enlarged follicles (12%), menorrhagia (6%), breast pain/tenderness (5%), ovarian cysts

Gastrointestinal: Abdominal pain (12%)

Genitourinary: Uterine/vaginal bleeding alterations (52%), intermenstrual bleeding/spotting (23%), pelvic pain (13%), leukorrhea (5%)

Miscellaneous: Ectopic pregnancy ( $\leq 50\%$ ), IUD expulsion (5%)

<5%: Abdominal distension, alopecia, anemia, back pain, cervicitis, dysmenorrhea, dyspareunia, eczema, edema, hirsutism, hypertension, libido decreased, nausea, nervousness, pruritus, rash, urticaria, vaginitis, weight gain

Postmarketing and/or case reports: Angioedema, device breakage, failed insertion, sepsis

Oral tablets:

>10%:

Central nervous system: Fatigue (13% to 17%), headache (10% to 17%), dizziness (10% to 11%)

Endocrine & metabolic: Heavier menstrual bleeding (14% to 31%), lighter menstrual bleeding (12%), breast tenderness (8% to 11%)

Gastrointestinal: Nausea (14% to 23%), abdominal pain (13% to 18%)

1% to 10%:

Endocrine & metabolic: Menses delayed (5%)

Gastrointestinal: Vomiting (6%), diarrhea (5%)

Postmarketing and/or case reports: Dysmenorrhea, menstruation irregularities, oligomenorrhea, pelvic pain

Metabolism/Transport Effects

Substrate of CYP3A4 (major); Note: Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential

Drug Interactions

Acitretin: May diminish the therapeutic effect of Contraceptives (Progestins). Contraceptive failure is possible. Management: Given the potential for progestin-only preparations to fail to prevent pregnancy during acitretin therapy, such products should not be relied upon. Alternative, nonhormonal forms of contraception must be employed during acitretin therapy. Risk D: Consider therapy modification

Aminoglutethimide: May increase the metabolism of Progestins. Management: Progestin-containing contraceptives are not recommended; consider the use of alternative, nonhormonal contraceptives. Risk D: Consider therapy modification

Aprepitant: May decrease the serum concentration of Contraceptives (Progestins). Management: Alternative or additional methods of contraception should be used both during treatment with aprepitant or fosaprepitant and for at least one month following the last aprepitant/fosaprepitant



dose. Risk D: Consider therapy modification

Artemether: May decrease the serum concentration of Contraceptives (Progestins). Management: Consider the use of an alternative (i.e., non-hormonal) means of contraception in all women of childbearing potential who are using artemether. Risk D: Consider therapy modification

Barbiturates: May diminish the therapeutic effect of Contraceptives (Progestins). Contraceptive failure is possible. Management: Use of alternative, nonhormonal contraceptives is recommended. Risk D: Consider therapy modification

Benzodiazepines (metabolized by oxidation): Contraceptives (Progestins) may increase the serum concentration of Benzodiazepines (metabolized by oxidation). Risk C: Monitor therapy

Bexarotene: May decrease the serum concentration of Contraceptives (Progestins). Management: Women of childbearing potential receiving bexarotene should use two reliable forms of contraception (including at least one nonhormonal form). Risk D: Consider therapy modification

Bexarotene (Systemic): May decrease the serum concentration of Contraceptives (Progestins). Management: Women of childbearing potential receiving bexarotene should use two reliable forms of contraception (including at least one nonhormonal form). Risk D: Consider therapy modification

Bile Acid Sequestrants: May decrease the serum concentration of Contraceptives (Progestins). Management: Administer oral progestin-containing contraceptives at least 1-4 hours prior to or 4-6 hours after administration of a bile acid sequestrant. Risk D: Consider therapy modification

Boceprevir: May increase the serum concentration of Contraceptives (Progestins). Management: Do not rely on systemic hormonal contraceptives for contraception during treatment with boceprevir. Patients receiving combination regimens containing ribavirin should use two alternative effective means of contraception. Risk D: Consider therapy modification

Bosentan: May decrease the serum concentration of Contraceptives (Progestins). Management: Use an alternative (i.e., non-hormonal) means of contraception for all women of childbearing potential who are using bosentan, and do not rely on hormonal contraceptives alone. Risk D: Consider therapy modification

Carbamazepine: May diminish the therapeutic effect of Contraceptives (Progestins). Contraceptive failure is possible. Management: Use of alternative, nonhormonal contraceptives is recommended. Risk D: Consider therapy modification

Clobazam: May decrease the serum concentration of Contraceptives (Progestins). Risk D: Consider therapy modification

Conivaptan: May increase the serum concentration of CYP3A4 Substrates (Low risk). Risk C: Monitor therapy

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. Risk C: Monitor therapy

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. Risk C: Monitor therapy

Felbamate: May decrease the serum concentration of Contraceptives (Progestins). Management: Contraceptive failure is possible. Use of an alternative, nonhormonal method of contraception is recommended. Risk D: Consider therapy modification

Fosaprepitant: May decrease the serum concentration of Contraceptives (Progestins). The active metabolite aprepitant is likely responsible for this effect. Management: Alternative or additional methods of contraception should be used both during treatment with aprepitant or fosaprepitant and for at least one month following the last aprepitant/fosaprepitant dose. Risk D: Consider therapy modification

Fosphenytoin: May diminish the therapeutic effect of Contraceptives (Progestins). Contraceptive failure is possible. Management: Contraceptive failure is possible. Use of an alternative, nonhormonal contraceptive is recommended. Risk D: Consider therapy modification

Griseofulvin: May diminish the therapeutic effect of Contraceptives (Progestins). Contraceptive failure is possible. Risk X: Avoid combination

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. Risk C: Monitor therapy

Lamotrigine: May decrease the serum concentration of Contraceptives (Progestins). Management: Women using progestin-only "minipill" products may be at risk for contraceptive failure; it is unclear if other progestin-containing products would be significantly impacted. Alternative, non-hormonal, means of contraception are recommended. Risk D: Consider therapy modification

Mycophenolate: May decrease the serum concentration of Contraceptives (Progestins). Management: Use of an additional or alternative (nonhormonal) method of contraception should be considered. Risk D: Consider therapy modification

Nevirapine: May decrease the serum concentration of Contraceptives (Progestins). Risk D: Consider therapy modification

Oxcarbazepine: May decrease the serum concentration of Contraceptives (Progestins). Management: Contraceptive failure is possible. Use of an additional or alternative, nonhormonal method of contraception is recommended. Risk D: Consider therapy modification

Phenytoin: May diminish the therapeutic effect of Contraceptives (Progestins). Contraceptive failure is possible. Management: Contraceptive failure is possible. Use of an alternative, nonhormonal contraceptive is recommended. Risk D: Consider therapy modification

Retinoic Acid Derivatives: May diminish the therapeutic effect of Contraceptives (Progestins). Retinoic Acid Derivatives may decrease the serum concentration of Contraceptives (Progestins). Management: Two forms of effective contraception should be used in patients receiving retinoic acid derivatives. Particularly, microdosed progesterone-only preparations may be inadequately effective. Risk D: Consider therapy modification

Rifamycin Derivatives: May decrease the serum concentration of Contraceptives (Progestins). Contraceptive failure is possible. Management: Contraceptive failure is possible. Use of an alternative, nonhormonal contraceptive is recommended. Risk D: Consider therapy modification

Selegiline: Contraceptives (Progestins) may increase the serum concentration of Selegiline. Risk C: Monitor therapy

St John's Wort: May diminish the therapeutic effect of Contraceptives (Progestins). Contraceptive failure is possible. Management: Consider using a product other than St John's wort. Contraceptive failure is possible. Use of an alternative, nonhormonal contraceptive is recommended. Risk D: Consider therapy modification

Telaprevir: May decrease the serum concentration of Contraceptives (Progestins). Management: Two different nonhormonal forms of contraception are required for women of childbearing potential taking telaprevir. Hormonal contraceptives may be less effective during concurrent telaprevir and for up to 2 weeks after telaprevir discontinuation. Risk D: Consider therapy modification

Tocilizumab: May decrease the serum concentration of CYP3A4 Substrates. Risk C: Monitor therapy

Topiramate: May decrease the serum concentration of Contraceptives (Progestins). Management: Caution patients that this combination may be associated with reduced contraceptive effectiveness. Consider adding an additional (non-hormonal) contraceptive method. Risk D: Consider therapy modification

Tranexamic Acid: Contraceptives (Progestins) may enhance the thrombogenic effect of Tranexamic Acid. Management: Ensure that the potential benefits of concurrent therapy outweigh the increased risk of potential thrombosis that accompanies use of tranexamic acid with hormonal contraceptives. Risk D: Consider therapy modification

Vitamin K Antagonists (eg, warfarin): Contraceptives (Progestins) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. Management: When possible, concomitant hormonal contraceptives and coumarin derivatives should be avoided in order to eliminate the risk of thromboembolic disorders. Consider using an alternative, nonhormonal contraceptive. Risk D: Consider therapy modification

Voriconazole: May increase the serum concentration of Contraceptives (Progestins). Contraceptives (Progestins) may increase the serum concentration of Voriconazole. Risk C: Monitor therapy  
Ethanol/Nutrition/Herb Interactions

Herb/Nutraceutical: St John's wort (an enzyme inducer) may decrease serum levels of levonorgestrel.  
Test Interactions

Decreased concentrations of sex hormone-binding globulin; decreased thyroxine concentrations (slight); increased triiodothyronine uptake  
Monitoring Parameters

IUD: Re-examine 4-12 weeks following insertion and then yearly. Threads should be visible; if length of thread has changed device may have become displaced, broken, perforated the uterus, or expelled. Transvaginal ultrasound may be used to check placement. Monitor for prolonged menstrual bleeding, amenorrhea, irregularity of menses, Pap smear, blood pressure, serum glucose in patients with diabetes, LDL levels in patients with hyperlipidemias; re-examine following first menses postinsertion of IUD. Patients presenting with lower abdominal pain should be evaluated for follicular atresia and ectopic pregnancy. Signs of infection following IUD insertion, especially in patients at increased risk (eg, patients on chronic corticosteroids, patients with type 1 diabetes mellitus).

Oral tablet: Evaluate for pregnancy, spontaneous abortion or ectopic pregnancy if menses is delayed for  $\geq 1$  week following emergency contraception, or if lower abdominal pain or persistent irregular bleeding develops.  
Reference Range

Intrauterine device: Plasma levels range from 150-200 pg/mL which are lower than those observed with other dosage forms of levonorgestrel

Nursing: Physical Assessment/Monitoring

Pregnancy should be ruled out prior to insertion of IUD. Monitor for prolonged menstrual bleeding, amenorrhea, and irregularity of menses. Caution patient about need for annual medical exams.

Monitoring: Lab Tests

IUD: Monitor serum glucose in patients with diabetes, LDL levels in patients with hyperlipidemias  
Patient Education

This drug does not protect against HIV infection or other sexually-transmitted diseases. Cigarette smoking is not recommended. You may experience cramping, headache, abdominal discomfort, hair loss, weight changes, or unusual menses (breakthrough bleeding, irregularity, excessive bleeding). Report sudden acute headache or visual disturbance, unusual nausea or vomiting, any loss of feeling in arms or legs, or lower abdominal pain.

Intrauterine device: This method provides up to 5 years of birth control. It will be inserted and removed by your prescriber. Notify your prescriber if the system comes out by itself or if you have heavy bleeding, unusual vaginal discharge, low abdominal pain, painful sexual intercourse, chills, or fever. There is an increased risk of ectopic pregnancy with this product. Thread placement should be checked following each menstrual cycle; do not pull thread.

Tablet: This method provides emergency contraception. It is used after your normal form of birth control has failed or following unprotected sexual intercourse. It should be used within 72 hours. Contact prescriber if you vomit within 2 hours of taking either dose.

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Intrauterine device, intrauterine:

Mirena®: 52 mg/device [releases levonorgestrel 20 mcg/day]

Tablet, oral: 0.75 mg

Next Choice™: 0.75 mg

Plan B® One Step: 1.5 mg  
Generic Available (U.S.)

Yes: Tablet

Mechanism of Action

Pregnancy may be prevented through several mechanisms: Thickening of cervical mucus, which inhibits sperm passage through the uterus and sperm survival; inhibition of ovulation, from a negative feedback mechanism on the hypothalamus, leading to reduced secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH); and inhibition of implantation.

Levonorgestrel is not effective once the implantation process has begun.

Pharmacodynamics/Kinetics

Duration: Intrauterine device: Up to 5 years

Absorption: Oral: Rapid and complete

Distribution: Vd: ~1.8 L/kg

Protein binding: Highly bound to albumin (~50%) and sex hormone-binding globulin (~47%)

Metabolism: To inactive metabolites

Half-life elimination: Oral: ~24 hours

Time to peak: Oral: ~2 hours

Excretion: Urine (45%); feces (32%)

Pharmacogenomic Genes of Interest

BRCA Genes

CYP3A4

Prothrombin

Local Anesthetic/Vasoconstrictor Precautions

No information available to require special precautions

Effects on Dental Treatment

No significant effects or complications reported

Effects on Bleeding

No information available to require special precautions

Related Information

Contraceptive Comparison

Pharmacotherapy Pearls

Intrauterine device: The cumulative 5-year pregnancy rate is ~0.7 pregnancies/100 users. Over 70% of women in the trials had previously used IUDs. The reported pregnancy rate after 12 months was  $\leq 0.2$  pregnancies/100 users. Approximately 80% of women who wish to conceive have become pregnant within 12 months of device removal. The recommended patient profile for this product: A woman who has at least one child, is in a stable and mutually-monogamous relationship, no history of pelvic inflammatory disease, and no history of ectopic pregnancy or predisposition to ectopic pregnancy. Keep a copy of the consent form and record lot number of device.

Oral tablet: Treatment for emergency contraception should begin as soon as possible; however, treatment is still moderately effective if used within 5 days and should be made available to women up to 5 days after unprotected or inadequately protected intercourse. May be used in women with contraindications to conventional oral contraceptive agents (eg, cardiovascular disease, migraines, liver disease). When used as directed for emergency contraception, the expected pregnancy rate is decreased from 8% to 1%. Approximately 87% of women have their next menstrual period at approximately the expected time. A rapid return to fertility following use is expected. When using the two-dose emergency contraceptive regimen, the second dose is equally effective if taken 12-24 hours after the first.

Mental Health: Effects on Mental Status

May cause nervousness or dizziness

Mental Health: Effects on Psychiatric Treatment

Carbamazepine may decrease the effects of levonorgestrel

Index Terms

LNg 20; Plan B  
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International Brand Names

Ange 28 (JP); duofem (DE); ECEEZ (IN); Escapelle (CL); Glanique (EC); Imediat N (UY); Jadelle (NZ, TH); Levonelle (GB, IE, NZ); Levonelle-2 (AU); Levonova (SE); Levostrel (TW); Madonna (MY); Microlut (CO, LU); Microval (LU); Mirena (AR, AT, AU, BB, BE, BG, BM, BS, BZ, CH, CO, CR, CZ, DE, DO, EC, ES, GB, GT, GY, HK, HN, HU, ID, IE, IL, IT, JM, KP, LU, MY, NI, NL, NZ, PA, PE, PH, PR, RU, SR, SV, TT, UY, ZA); Norlevo (AU, DK, ES, FI, FR, GR, IL, IN, KP, NO, PT, SE, TR, ZA); Norplant (CL, LU, PH, TH, TW); Pill 72 (HK); Plan B (DO, HN, NI, SV); Postinor (BE, CH, CL, EE, HU, PL, SE); Postinor-1 (AU, NZ); Postinor-2 (AU, BR, CN, HK, MX, PE, SG, TW, VE); Pronta (PY); Rigesoft (HU); Safe Plan (TW)

Disclaimer:

Readers are advised that decisions regarding drug therapy must be based on the independent judgment of the clinician, changing information about a drug (eg, as reflected in the literature and manufacturer's most current product information), and changing medical practices.

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Ulipristal  
(Lexi-Drugs)  
Pronunciation

(ue li PRIS tal)  
Brand Names: U.S.

ella®  
Pharmacologic Category

Contraceptive; Progestin Receptor Modulator  
Dosing: Adult

Emergency contraception: Oral: One tablet (30 mg) as soon as possible, but within 120 hours (5 days) of unprotected intercourse or contraceptive failure

\* See Dosage and Administration in AHFS Essentials for additional information.  
Dosing: Geriatric

Not indicated for use in postmenopausal women.  
Dosing: Pediatric

Not for use prior to menarche.  
Use: Labeled Indications

Emergency contraception following unprotected intercourse or possible contraceptive failure

\* See Uses in AHFS Essentials for additional information.  
Clinical Practice Guidelines

CDC, "U.S. Medical Eligibility Criteria for Contraceptive Use, 2010," May 2010  
Administration: Oral

Administer with or without food at anytime during menstrual cycle. If vomiting occurs within 3 hours of administration, consider repeating dose.  
Dietary Considerations

May be taken with or without food.  
Storage

Store at 20°C to 25°C (68°F to 77°F). Protect from light.

Medication Safety Issues  
Sound-alike/look-alike issues:  
Contraindications

Known or suspected pregnancy  
Warnings/Precautions

Concerns related to adverse effects:

- Bleeding irregularities: Menstrual bleeding patterns may be altered (cycle length may be delayed or shortened by a few days), but returns to normal in subsequent cycles. Intermenstrual bleeding (spotting) has also been observed. The possibility of pregnancy should be considered if menstruation is delayed for >7 days of the expected menstrual period.
- Ectopic pregnancy: A history of ectopic pregnancy is not a contraindication to use in emergency

contraception. The possibility of ectopic pregnancy should be considered in patients with abdominal pain after administration of ulipristal.

Disease related concerns:

- Hepatic impairment: Safety and efficacy have not been established for use in hepatic impairment.
- Renal impairment: Safety and efficacy have not been established for use in renal impairment.

Special populations:

- Pediatrics: Not for use prior to menarche.
- Postmenopausal women: Not indicated for use in postmenopausal women.

Other warnings/precautions:

- Appropriate use: Not intended for routine contraception. Repeated use within the same menstrual cycle is not recommended.
- Fertility: Oral tablet: Barrier contraception is recommended immediately following emergency contraception and throughout the same menstrual cycle; efficacy of hormonal contraception may be decreased.
- HIV infection protection: Does not protect against HIV infection or other sexually-transmitted diseases.
- Pregnancy: Exclude pregnancy prior to therapy via history, physical exam or pregnancy testing; not indicated for terminating an existing pregnancy.

\* See Cautions in AHFS Essentials for additional information.

Pregnancy Risk Factor

X

Pregnancy Considerations

Embryofetal loss was observed following administration of ulipristal to pregnant rats and rabbits during the period of organogenesis at doses that were 1/3 and 1/2 the human dose (based on BSA), respectively. Teratogenic effects were not observed in surviving fetuses. Pregnancy terminations were also observed in pregnant monkeys following administration of ulipristal during the first trimester in doses ~3 times the human dose (based on BSA). Exclude pregnancy prior to therapy; not indicated for terminating an existing pregnancy. A rapid return of fertility is expected following use for emergency contraception; routine contraceptive measures should be initiated or continued following use to ensure ongoing prevention of pregnancy. Barrier contraception is recommended immediately following emergency contraception and throughout the same menstrual cycle; efficacy of hormonal contraceptives may be decreased.

Lactation

Excretion unknown/not recommended

Adverse Reactions

>10%:

Central nervous system: Headache (18% to 19%)



Endocrine & metabolic: Menstruation occurring  $\geq 7$  days later than expected (19%), dysmenorrhea (7% to 13%)

Gastrointestinal: Abdominal pain (8% to 15%), nausea (12% to 13%)

1% to 10%:

Central nervous system: Fatigue (6%), dizziness (5%)

Endocrine & metabolic: Intermenstrual bleeding (9%), menstruation occurring  $\geq 7$  days earlier than expected (7%)

Postmarketing and/or case reports: Acne

\* See Cautions in AHFS Essentials for additional information.

Metabolism/Transport Effects

Substrate of CYP3A4 (major); Note: Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential  
Drug Interactions

Conivaptan: May increase the serum concentration of CYP3A4 Substrates (Low risk). Risk C: Monitor therapy

CYP3A4 Inducers (Strong): May decrease the serum concentration of Ulipristal. Risk C: Monitor therapy

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. Risk C: Monitor therapy

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. Risk C: Monitor therapy

Tocilizumab: May decrease the serum concentration of CYP3A4 Substrates. Risk C: Monitor therapy

Ethanol/Nutrition/Herb Interactions

Herb/Nutraceutical: St John's wort (an enzyme inducer) may decrease serum levels of ulipristal.  
Monitoring Parameters

Evaluate for pregnancy or ectopic pregnancy if menses is delayed for  $\geq 1$  week following emergency contraception, or if lower abdominal pain (3-5 weeks after administration) or persistent irregular bleeding develops.

Monitoring: Lab Tests

Evaluate for pregnancy or ectopic pregnancy if menses is delayed for  $\geq 1$  week following emergency contraception, or if lower abdominal pain (3-5 weeks after administration) or persistent irregular bleeding develops.

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, oral, as acetate:

ella®: 30 mg

Generic Available (U.S.)

No

Mechanism of Action

Prevents progestin from binding to the progesterone receptor. Ulipristal postpones follicular rupture when administered prior to ovulation, thereby inhibiting or delaying ovulation. May also alter the normal endometrium, impairing implantation.

Pharmacodynamics/Kinetics

Protein binding: Ulipristal: >94% to plasma proteins including albumin, alpha1-acid glycoprotein, and high-density lipoprotein

Metabolism: Hepatic via CYP3A4; forms monodemethylated metabolite (active) and inactive metabolites

Half-life elimination: Ulipristal: ~32 hours; Monodemethylated metabolite: ~27 hours

Time to peak, serum: 1 hour (ulipristal and monodemethylated metabolite)

Local Anesthetic/Vasoconstrictor Precautions

No information available to require special precautions

Effects on Dental Treatment

No significant effects or complications reported

Effects on Bleeding

No information available to require special precautions

Related Information

Contraceptive Comparison

Mental Health: Effects on Mental Status

May cause fatigue and dizziness

Mental Health: Effects on Psychiatric Treatment

St John's wort may decrease levels of ulipristal

Index Terms

CDB-2914; Ulipristal Acetate

References

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Glasier AF, Cameron ST, Fine PM, et al, "Ulipristal Acetate Versus Levonorgestrel for Emergency Contraception: A Randomised Non-Inferiority Trial And Meta-Analysis," *Lancet*, 2010, 375(9714):555-62.[PubMed 20116841]

International Brand Names

Ella (IL, SG); ellaOne (BE, CZ, DK, EE, FR, GB, HN, KP, NL, NO, PT, SE)

Disclaimer:

Readers are advised that decisions regarding drug therapy must be based on the independent judgment of the clinician, changing information about a drug (eg, as reflected in the literature and

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Ethinyl Estradiol and Norethindrone  
(Lexi-Drugs)  
ALERT: U.S. Boxed Warning

The FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or [www.fda.gov](http://www.fda.gov).  
Pronunciation

(ETH in il es tra DYE ole & nor eth IN drone)  
Brand Names: U.S.

Aranelle®; Balziva™; Brevicon®; Cyclofem™ 1/35; Cyclofem™ 7/7/7; Estrostep® Fe; Femcon® Fe; femhrt®; femhrt® Lo; Generess™ Fe; Gildess® FE 1.5/30; Gildess® FE 1/20; Jevantique™; Jinteli™; Junel® 1.5/30; Junel® 1/20; Junel® Fe 1.5/30; Junel® Fe 1/20; Leena®; Lo Loestrin™ Fe; Loestrin® 21 1.5/30; Loestrin® 21 1/20; Loestrin® 24 Fe; Loestrin® Fe 1.5/30; Loestrin® Fe 1/20; Microgestin® 1.5/30; Microgestin® 1/20; Microgestin® Fe 1.5/30; Microgestin® Fe 1/20; Modicon®; Necon® 0.5/35; Necon® 1/35; Necon® 10/11; Necon® 7/7/7; Norinyl® 1+35; Nortrel® 0.5/35; Nortrel® 1/35; Nortrel® 7/7/7; Ortho-Novum® 1/35; Ortho-Novum® 7/7/7; Ovcon® 35; Ovcon® 50; Tilia™ Fe; Tri-Legest™ Fe; Tri-Norinyl®; Zenchent Fe™; Zenchent™; Zeosa™  
Brand Names: Canada

Brevicon® 0.5/35; Brevicon® 1/35; FemHRT®; Loestrin™ 1.5/30; Minestrin™ 1/20; Ortho® 0.5/35; Ortho® 1/35; Ortho® 7/7/7; Select™ 1/35; Synphasic®  
Pharmacologic Category

Contraceptive; Estrogen and Progestin Combination  
Dosing: Adult

Adolescents ≥15 years and Adults: Females: Acne: Estrostep® Fe: Oral: Refer to dosing for contraception

Moderate-to-severe vasomotor symptoms associated with menopause: Initial: femhrt® 0.5/2.5: Oral: 1 tablet daily; patient should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary; patient should be maintained on lowest effective dose

Prevention of osteoporosis: Initial: femhrt® 0.5/2.5: Oral: 1 tablet daily; patient should be maintained on lowest effective dose

Contraception: Oral:

Schedule 1 (Sunday starter): Dose begins on first Sunday after onset of menstruation; if the menstrual period starts on Sunday, take first tablet that very same day. This schedule is not preferred for Lo Loestrin™ Fe. With a Sunday start, an additional method of contraception should be used until after the first 7 days of consecutive administration (all products).

For 21-tablet package: Dosage is 1 tablet daily for 21 consecutive days, followed by 7 days off of the medication; a new course begins on the 8th day after the last tablet is taken.

For 28-tablet package: Dosage is 1 tablet daily without interruption.

Schedule 2 (Day 1 starter): Dose starts on first day of menstrual cycle taking 1 tablet daily.

For 21-tablet package: Dosage is 1 tablet daily for 21 consecutive days, followed by 7 days off of the medication; a new course begins on the 8th day after the last tablet is taken.

For 28-tablet package: Dosage is 1 tablet daily without interruption.

If all doses have been taken on schedule and one menstrual period is missed, continue dosing cycle. If two consecutive menstrual periods are missed, pregnancy test is required before new dosing cycle is started.

Missed doses monophasic formulations (refer to package insert for complete information):

One dose missed: Take as soon as remembered. Take the next tablet at your regular time. You may take 2 tablets in 1 day.

Two consecutive doses missed in the first 2 weeks: Take 2 tablets as soon as remembered and 2 tablets the next day. An additional method of contraception should be used for 7 days after missed dose.

Two consecutive doses missed in week 3 (all products) or in week 4 (Lo Loestrin™ Fe), or three consecutive doses missed at any time (all products): An additional method of contraception must be used for 7 days after a missed dose.

Schedule 1 (Sunday starter): Continue dose of 1 tablet daily until Sunday, then discard the rest of the pack, and a new pack should be started that same day.

Schedule 2 (Day 1 starter): Current pack should be discarded, and a new pack should be started that same day.

Missed doses biphasic/triphasic formulations (refer to package insert for complete information):

One dose missed: Take as soon as remembered. Take the next tablet at your regular time. You may take 2 tablets in 1 day.

Two consecutive doses missed in week 1 or week 2 of the pack: Take 2 tablets as soon as remembered and 2 tablets the next day. Resume taking 1 tablet daily until the pack is empty. An additional method of contraception should be used for 7 days after a missed dose.

Two consecutive doses missed in week 3 of the pack: An additional method of contraception must be used for 7 days after a missed dose.

Schedule 1 (Sunday Starter): Take 1 tablet every day until Sunday. Discard the remaining pack and start a new pack of pills on the same day.

Schedule 2 (Day 1 starter): Discard the remaining pack and start a new pack the same day.

Three or more consecutive doses missed: An additional method of contraception must be used for 7 days after a missed dose.

Schedule 1 (Sunday Starter): Take 1 tablet every day until Sunday; on Sunday, discard the pack and start a new pack.

Schedule 2 (Day 1 Starter): Discard the remaining pack and begin new pack of tablets starting on the same day.

Switching from a different contraceptive:

Oral contraceptive: Start on the same day that a new pack of the previous oral contraceptive would have been taken.

Transdermal patch, vaginal ring, injection: Start on the day the next dose would have been due.

IUD or implant: Start on the day of removal. A backup method of contraception may be required following IUD removal.

Use after childbirth (in women who are not breast-feeding) or after second trimester abortion: Therapy may be started  $\geq 4$  weeks postpartum. Pregnancy should be ruled out prior to treatment if menstrual periods have not restarted and an additional method of contraception (nonhormonal) should be used until after the first 7 days of consecutive administration.

Dosing: Geriatric

Refer to adult dosing.

Dosing: Pediatric

Females:

Acne: Oral (Eloestrel® Fe): For use in females  $\geq 15$  years; refer to adult dosing for contraception

Contraception: Oral: Refer to adult dosing; not to be used prior to menarche.

Dosing: Renal Impairment

Specific guidelines not available; use with caution and monitor blood pressure closely. Consider other forms of contraception.

Dosing: Hepatic Impairment

Contraindicated in patients with hepatic impairment.

Use: Labeled Indications

Prevention of pregnancy; treatment of acne; moderate-to-severe vasomotor symptoms associated with menopause; prevention of osteoporosis (in women at significant risk only)

Use: Unlabeled

Treatment of hypermenorrhea (menorrhagia); pain associated with endometriosis, dysmenorrhea; dysfunctional uterine bleeding

Clinical Practice Guidelines

CDC, "U.S. Medical Eligibility Criteria for Contraceptive Use, 2010," MMWR, May 2010

CDC, "U.S. Medical Eligibility Criteria for Contraceptive Use, 2010, Update" MMWR, July 2011

Administration: Oral

Administer at the same time each day; without regard to meals.

Lo Loestrin™ Fe: If vomiting or diarrhea occurs within 3-4 hours of a dose, consider the dose to be missed.

Dietary Considerations

Should be taken at same time each day. May be taken without regard to meals. Ensure adequate calcium and vitamin D intake when used for the prevention of osteoporosis.

Storage

Store at controlled room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Eloestrel® Fe: Protect from light.

Medication Safety Issues

Sound-alike/look-alike issues:  
Contraindications

Hypersensitivity to ethinyl estradiol, norethindrone, norethindrone acetate, or any component of the formulation; breast cancer or other estrogen- or progestin-dependent neoplasms (current or a history of), hepatic tumors or disease, pregnancy, undiagnosed abnormal uterine bleeding

Use is also contraindicated in women at high risk of arterial or venous thrombotic diseases including: Cerebrovascular disease, coronary artery disease, diabetes mellitus with vascular disease, DVT or PE (current or history of), hypercoagulopathies (inherited or acquired), headaches with focal neurological symptoms, hypertension (uncontrolled), migraine headaches if >35 years of age, thrombogenic valvular or rhythm diseases of the heart (eg, subacute bacterial endocarditis with valvular disease or atrial fibrillation), women >35 years of age who smoke.  
Warnings/Precautions

Boxed warnings:

- Cardiovascular disease: See “Disease-related concerns” below.
- Dementia: See “Concerns related to adverse effects” below.
- Risks vs benefits: See “Other warnings/precautions” below.
- Smokers: See “Special populations” below.

Concerns related to adverse effects:

- Angioedema: Estrogens may induce or exacerbate symptoms in women with hereditary angioedema.
- Breast cancer: Estrogens may increase the risk of breast cancer. The use of combination hormonal contraceptives has been associated with a slight increase in frequency of breast cancer, however studies are not consistent. Use for contraception is contraindicated in women with (or history of) breast cancer. An increased risk of invasive breast cancer was observed in postmenopausal women using conjugated estrogens (CE) in combination with medroxyprogesterone acetate (MPA); a smaller increase in risk was seen with estrogen therapy alone in observational studies. An increase in abnormal mammograms has also been reported with estrogen and progestin therapy in postmenopausal women. Estrogen use may lead to severe hypercalcemia in postmenopausal patients with breast cancer and bone metastases; discontinue estrogen if hypercalcemia occurs.
- Carbohydrate intolerance: May have adverse effects on glucose tolerance; use caution in women with diabetes.
- Chloasma: Use caution with a history of chloasma gravidarum; women with a tendency to chloasma should avoid sun and ultraviolet radiation exposure during therapy.
- Dementia: [U.S. Boxed Warning]: The risk of dementia may be increased in postmenopausal women; increased incidence was observed in women  $\geq 65$  years of age taking CE alone or in combination with MPA.
- Endometrial carcinoma: Adequate diagnostic measures, including endometrial sampling (if indicated), should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding. Unopposed estrogens may increase the risk of endometrial carcinoma in postmenopausal women with an intact uterus. Risk appears to be associated with long-term use. The use of a progestin should be considered when administering estrogens to postmenopausal

women with an intact uterus.

- **Lipid effects:** Combination hormonal contraceptives may affect serum triglyceride and lipoprotein levels. Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Progestins may be associated with decreased HDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.
- **Ovarian cancer:** Postmenopausal estrogen therapy and combined estrogen/progesterone therapy may increase the risk of ovarian cancer; however, the absolute risk to an individual woman is small. Although results from various studies are not consistent, risk does not appear to be significantly associated with the duration, route, or dose of therapy. In one study, the risk decreased after 2 years following discontinuation of therapy.
- **Retinal vascular thrombosis:** Estrogens may cause retinal vascular thrombosis; discontinue if migraine, loss of vision, proptosis, diplopia or other visual disturbances occur; discontinue permanently if papilledema or retinal vascular lesions are observed on examination.
- **Thromboembolism:** May increase the risk of thromboembolism; discontinue use of combination hormonal contraceptives if an arterial or venous thrombotic event occurs.
- **Vaginal bleeding:** Unscheduled bleeding/spotting may occur within the first 3 months of combination oral contraceptive use. Presentation of irregular, unresolving vaginal bleeding following previously regular cycles warrants further evaluation including endometrial sampling, if indicated, to rule out malignancy.

Disease-related concerns:

- **Cardiovascular disease:** [U.S. Boxed Warning]: Estrogens with or without progestin should not be used to prevent coronary heart disease. Use caution with cardiovascular disease or dysfunction. May increase the risks of myocardial infarction (MI), stroke, pulmonary emboli (PE), and deep vein thrombosis (DVT); incidence of these effects was shown to be significantly increased in postmenopausal women using CE in combination with MPA. Nonfatal MI, PE, and thrombophlebitis have also been reported in males taking high doses of CE (eg, for prostate cancer). Risk factors include diabetes mellitus, hypercholesterolemia, hypertension, SLE, obesity, and/or venous thromboembolism (VTE). When used for contraception, use with caution in patients with risk factors for cardiovascular disease (eg, hypertension, hypercholesterolemia, morbid obesity, diabetes, or women who smoke); may also lead to increased risk of cerebrovascular events (stroke). May have a dose-related risk of vascular disease and hypertension; women with hypertension should be encouraged to use another form of contraception. Monitor women with well-controlled hypertension and discontinue if blood pressure rises significantly. Use is contraindicated with uncontrolled hypertension.
- **Cholestatic jaundice:** Cholestasis may occur in women with a history of pregnancy-related or previous estrogen-related cholestasis.
- **Depression:** Use with caution in patients with depression.
- **Diseases exacerbated by fluid retention:** Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes, or renal dysfunction.
- **Endometriosis:** Estrogens may exacerbate endometriosis. Malignant transformation of residual endometrial implants has been reported posthysterectomy with estrogen only therapy. Consider adding a progestin in women with residual endometriosis posthysterectomy.



- Gallbladder disease: Use with caution in patients with gallbladder disease. May have a dose-related risk of gallbladder disease.
- Hepatic adenomas: Extremely rare adenomas and focal nodular hyperplasia resulting in fatal intra-abdominal hemorrhage have been reported in association with long-term oral contraceptive use. Presentation of an abdominal mass, acute abdominal pain, or intra-abdominal bleeding warrants further evaluation to rule out source.
- Hepatic dysfunction: Steroid hormones may be poorly metabolized in patients with hepatic dysfunction. Discontinue if jaundice develops or if acute or chronic hepatic disturbances occur. Use is contraindicated with hepatic disease.
- Hypocalcemia: Use with caution in patients with severe hypocalcemia.
- Inherited thrombophilia: When used in postmenopausal women, use caution in patients with known inherited thrombophilias (eg, protein C or S deficiency); may have increased risk of VTE (DeSancho, 2010). Use is contraindicated in patients with DVT or PE (current or history of). Contraceptive products are contraindicated in women with inherited or acquired hypercoagulopathies.
- Migraine: Use with caution in patients with a history of migraine. Evaluate new, recurrent, severe, or persistent headaches. Use of combination oral contraceptives is contraindicated in women with headaches with focal neurological symptoms or migraine headaches if >35 years of age.
- Porphyria: Use with caution in patients with porphyria.
- Renal impairment: Women with renal disease should be encouraged to use a nonhormonal form of contraception.
- SLE: Use with caution in patients with SLE.

#### Special populations:

- Pediatrics: Combination hormonal contraceptives are not for use prior to menarche.
- Smokers: [U.S. Boxed Warning]: The risk of cardiovascular side effects is increased in women who smoke cigarettes; risk increases with age (especially women >35 years of age) and the number of cigarettes smoked; women who use combination hormonal contraceptives should be strongly advised not to smoke. Use is contraindicated in patients >35 years of age who smoke.
- Surgical patients: Whenever possible, should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

#### Dosage form specific issues:

- Lo Loestrin™ Fe: Safety and efficacy have not been established in women with a BMI >35 kg/m<sup>2</sup>.

#### Other warnings/precautions:

- Acne use: When used for acne, use only in females ≥15 years, who also desire combination hormonal contraceptive therapy, are unresponsive to topical treatments, have no contraindications to combination hormonal contraceptive use, and plan to stay on therapy for ≥6 months.

- HIV infection protection: Combination hormonal contraceptives do not protect against HIV infection or other sexually-transmitted diseases.
  - Minimum effective dosage: Combination hormonal contraceptives: The minimum dosage combination of estrogen/progestin that will effectively treat the individual patient should be used. New patients should be started on products containing  $\leq 0.035$  mg of estrogen per tablet.
  - Osteoporosis use: For use only in women at significant risk of osteoporosis and for who other non-estrogen medications are not considered appropriate.
  - Risks vs benefits: [U.S. Boxed Warning]: Estrogens with or without progestin should be used for the shortest duration possible at the lowest effective dose consistent with treatment goals. Before prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of progestin when added to estrogen therapy. Patients should be reevaluated as clinically appropriate to determine if treatment is still necessary. Available data related to treatment risks are from Women's Health Initiative (WHI) studies, which evaluated oral CE 0.625 mg with or without MPA 2.5 mg relative to placebo in postmenopausal women. Other combinations and dosage forms of estrogens and progestins were not studied. Outcomes reported from clinical trials using CE with or without MPA should be assumed to be similar for other doses and other dosage forms of estrogens and progestins until comparable data becomes available.
- Pregnancy Risk Factor

X

#### Pregnancy Considerations

Pregnancy should be ruled out prior to treatment and discontinued if pregnancy occurs. In general, the use of combination hormonal contraceptives when inadvertently taken early in pregnancy have not been associated with teratogenic effects. Hormonal contraceptives may be less effective in obese patients. An increase in oral contraceptive failure was noted in women with a BMI  $>27.3$  kg/m<sup>2</sup>. Similar findings were noted in patients weighing  $\geq 90$  kg (198 lb) using the contraceptive patch.

Due to increased risk of venous thromboembolism (VTE) postpartum, combination hormonal contraceptives should not be started in any woman  $<21$  days following delivery. Women without risk factors for VTE and who are not breast-feeding may start combination hormonal contraceptives during 21-42 days postpartum. After 42 days postpartum, restrictions for use are not related to postpartum status and should be based on other medical conditions (CDC, 2011). May be started immediately following first trimester abortion or miscarriage.

Lactation

Enters breast milk/not recommended

#### Breast-Feeding Considerations

Jaundice and breast enlargement in the nursing infant have been reported following the use of combination hormonal contraceptives. May decrease the quality and quantity of breast milk; alternative form of contraception is recommended (per manufacturer). The theoretical concerns about decreased milk production are greatest early in the postpartum period when milk production is being established. Postpartum risk status for VTE should be considered when initiating combination hormonal contraceptives after delivery. Combined hormonal contraceptives should not be started  $<21$  days postpartum due to increased risk of VTE. Risk of VTE is still elevated in breast-feeding women until  $\sim 42$  days postpartum and is greater in women with additional risk factors. After 42 days postpartum, restrictions for use are not related to postpartum VTE risk and should be based on other medical conditions (CDC, 2011).

Adverse Reactions

The following reactions have been associated with oral contraceptive use:

Increased risk or evidence of association with use:

Cardiovascular: Arterial thromboembolism, cerebral hemorrhage, cerebral thrombosis, hypertension, mesenteric thrombosis, MI, venous thrombosis (with or without embolism)

Gastrointestinal: Gallbladder disease

Hepatic: Hepatic adenomas, liver tumors (benign)

Local: Thrombophlebitis

Ocular: Retinal thrombosis

Renal: Impaired renal function

Respiratory: Pulmonary embolism

Adverse reactions considered drug related:

Cardiovascular: Edema, varicose vein aggravation

Central nervous system: Depression, migraine, mood changes

Dermatologic: Chloasma, melasma, rash (allergic)

Endocrine & metabolic: Amenorrhea, breakthrough bleeding, breast changes (enlargement, pain, secretion, tenderness), fluid retention, infertility (temporary), lactation decreased (with use immediately postpartum), menstrual flow changes, spotting

Gastrointestinal: Abdominal bloating, abdominal cramps, abdominal pain, appetite changes, nausea, weight changes, vomiting

Genitourinary: Cervical ectropion, cervical secretion, vaginal candidiasis, vaginitis

Hematologic: Folate decreased, porphyria exacerbation

Hepatic: Cholestatic jaundice

Neuromuscular & skeletal: Chorea exacerbation

Ocular: Contact lens intolerance, corneal curvature changes (steepening)

Miscellaneous: Anaphylactic/anaphylactoid reactions (including angioedema, circulatory collapse, respiratory collapse, urticaria), SLE exacerbation

Adverse reactions in which association is not confirmed or denied: Acne, Budd-Chiari syndrome, cataracts, colitis, cystitis-like syndrome, dizziness, dysmenorrhea, erythema multiforme, erythema nodosum, headache, hemolytic uremic syndrome, hemorrhagic eruption, hirsutism, libido changes, nervousness, optic neuritis (with or without partial or complete loss of vision), pancreatitis, premenstrual syndrome, renal function impaired, scalp hair loss

The following have been associated with femhrt® and in general, are similar to placebo. Also refer to adverse reactions observed with oral contraceptives for additional reactions observed

with estrogen/progestin therapy:

>10%: Central nervous system: Headache (15% to 18%)

1% to 10%:

Central nervous system: Depression (4% to 6%), nervousness (2% to 5%)

Endocrine & metabolic: Breast pain (8% to 9%)

Gastrointestinal: Abdominal pain (8% to 10%), nausea/vomiting (5% to 7%), diarrhea (4% to 6%), dyspepsia (3% to 5%)

Genitourinary: Urinary tract infection (4% to 6%), vaginitis (5%)

Respiratory: Sinusitis (8% to 9%)

Allergy and Idiosyncratic Reactions

Estrogen Allergy

Metabolism/Transport Effects

Refer to individual components.

Drug Interactions

Acitretin: May diminish the therapeutic effect of Contraceptives (Progestins). Contraceptive failure is possible. Management: Given the potential for progestin-only preparations to fail to prevent pregnancy during acitretin therapy, such products should not be relied upon. Alternative, nonhormonal forms of contraception must be employed during acitretin therapy. Risk D: Consider therapy modification

Aminoglutethimide: May increase the metabolism of Progestins. Management: Progestin-containing contraceptives are not recommended; consider the use of alternative, nonhormonal contraceptives. Risk D: Consider therapy modification

Anastrozole: Estrogen Derivatives may diminish the therapeutic effect of Anastrozole. Risk X: Avoid combination

Aprepitant: May decrease the serum concentration of Contraceptives (Estrogens). Management: Use of a non-hormone-based contraceptive is recommended. Risk D: Consider therapy modification

Aprepitant: May decrease the serum concentration of Contraceptives (Progestins). Management: Alternative or additional methods of contraception should be used both during treatment with aprepitant or fosaprepitant and for at least one month following the last aprepitant/fosaprepitant dose. Risk D: Consider therapy modification

ARIPiprazole: CYP3A4 Inhibitors (Weak) may increase the serum concentration of ARIPiprazole. Management: Monitor for increased aripiprazole systemic exposure/affects with concomitant use of a weak CYP3A4 inhibitor. Decrease aripiprazole dose to 25% of the usual dose in patients receiving both a CYP3A4 and a CYP2D6 inhibitor (regardless of potencies). Risk C: Monitor therapy

Armodafinil: May decrease the serum concentration of Contraceptives (Estrogens). Management: The manufacturer recommends that patients use nonhormonal contraceptives, in addition to or in place of hormonal contraceptives, during and for one month following treatment with armodafinil.

Risk D: Consider therapy modification

Artemether: May decrease the serum concentration of Contraceptives (Estrogens). Management: Consider the use of an alternative (i.e., non-hormonal) means of contraception in all women of childbearing potential who are using artemether. Risk D: Consider therapy modification

Artemether: May decrease the serum concentration of Contraceptives (Progestins). Management: Consider the use of an alternative (i.e., non-hormonal) means of contraception in all women of childbearing potential who are using artemether. Risk D: Consider therapy modification

Ascorbic Acid: May increase the serum concentration of Estrogen Derivatives. Risk C: Monitor therapy

Barbiturates: May diminish the therapeutic effect of Contraceptives (Estrogens). Contraceptive failure is possible. Management: Use of a non-hormonal contraceptive is recommended. Risk D: Consider therapy modification

Barbiturates: May diminish the therapeutic effect of Contraceptives (Progestins). Contraceptive failure is possible. Management: Use of alternative, nonhormonal contraceptives is recommended. Risk D: Consider therapy modification

Benzodiazepines (metabolized by oxidation): Contraceptives (Estrogens) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). Risk C: Monitor therapy

Benzodiazepines (metabolized by oxidation): Contraceptives (Progestins) may increase the serum concentration of Benzodiazepines (metabolized by oxidation). Risk C: Monitor therapy

Bexarotene: May decrease the serum concentration of Contraceptives (Estrogens). Management: Women of childbearing potential receiving bexarotene should use two reliable forms of contraception (including at least one nonhormonal form). Risk D: Consider therapy modification

Bexarotene: May decrease the serum concentration of Contraceptives (Progestins). Management: Women of childbearing potential receiving bexarotene should use two reliable forms of contraception (including at least one nonhormonal form). Risk D: Consider therapy modification

Bexarotene (Systemic): May decrease the serum concentration of Contraceptives (Estrogens). Management: Women of childbearing potential receiving bexarotene should use two reliable forms of contraception (including at least one nonhormonal form). Risk D: Consider therapy modification

Bexarotene (Systemic): May decrease the serum concentration of Contraceptives (Progestins). Management: Women of childbearing potential receiving bexarotene should use two reliable forms of contraception (including at least one nonhormonal form). Risk D: Consider therapy modification

Bile Acid Sequestrants: May decrease the serum concentration of Contraceptives (Estrogens). Management: Administer estrogen-based oral contraceptives at least 1-4 hours prior to or 4-6 hours after administration of a bile acid sequestrant. Risk D: Consider therapy modification

Bile Acid Sequestrants: May decrease the serum concentration of Contraceptives (Progestins). Management: Administer oral progestin-containing contraceptives at least 1-4 hours prior to or 4-6 hours after administration of a bile acid sequestrant. Risk D: Consider therapy modification

Boceprevir: May decrease the serum concentration of Contraceptives (Estrogens). Management: Do not rely on systemic hormonal contraceptives for contraception during treatment with

boceprevir. Patients receiving combination regimens containing ribavirin should use two alternative effective means of contraception. Risk D: Consider therapy modification

Boceprevir: May increase the serum concentration of Contraceptives (Progestins). Management: Do not rely on systemic hormonal contraceptives for contraception during treatment with boceprevir. Patients receiving combination regimens containing ribavirin should use two alternative effective means of contraception. Risk D: Consider therapy modification

Bosentan: May decrease the serum concentration of Contraceptives (Estrogens). Management: Use an alternative (i.e., non-hormonal) means of contraception for all women of childbearing potential who are using bosentan, and do not rely on hormonal contraceptives alone. Risk D: Consider therapy modification

Bosentan: May decrease the serum concentration of Contraceptives (Progestins). Management: Use an alternative (i.e., non-hormonal) means of contraception for all women of childbearing potential who are using bosentan, and do not rely on hormonal contraceptives alone. Risk D: Consider therapy modification

CarBAMazepine: May diminish the therapeutic effect of Contraceptives (Estrogens). Contraceptive failure is possible. Management: Use of a nonhormonal contraceptive is recommended. Risk D: Consider therapy modification

CarBAMazepine: May diminish the therapeutic effect of Contraceptives (Progestins). Contraceptive failure is possible. Management: Use of alternative, nonhormonal contraceptives is recommended. Risk D: Consider therapy modification

Chenodiol: Estrogen Derivatives may diminish the therapeutic effect of Chenodiol. Management: Monitor clinical response to chenodiol closely when used together with any estrogen derivative. Risk C: Monitor therapy

Clobazam: May decrease the serum concentration of Contraceptives (Estrogens). Risk D: Consider therapy modification

Clobazam: May decrease the serum concentration of Contraceptives (Progestins). Risk D: Consider therapy modification

Colesevelam: May decrease the serum concentration of Ethinyl Estradiol. Risk D: Consider therapy modification

Colesevelam: May decrease the serum concentration of Norethindrone. Risk D: Consider therapy modification

Conivaptan: May increase the serum concentration of CYP3A4 Substrates (Low risk). Risk C: Monitor therapy

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). Risk C: Monitor therapy

CYP1A2 Substrates: CYP1A2 Inhibitors (Moderate) may decrease the metabolism of CYP1A2 Substrates. Risk C: Monitor therapy

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. Risk C: Monitor therapy

Darunavir: May decrease the serum concentration of Norethindrone. Risk D: Consider therapy modification

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. Risk C: Monitor therapy

Felbamate: May decrease the serum concentration of Contraceptives (Estrogens). Contraceptive failure is possible. Management: Use of a nonhormonal contraceptive is recommended. Risk D: Consider therapy modification

Felbamate: May decrease the serum concentration of Contraceptives (Progestins). Management: Contraceptive failure is possible. Use of an alternative, nonhormonal method of contraception is recommended. Risk D: Consider therapy modification

Fosaprepitant: May decrease the serum concentration of Contraceptives (Estrogens). The active metabolite aprepitant is likely responsible for this effect. Management: Alternative or additional methods of contraception should be used both during treatment with fosaprepitant or aprepitant and for at least one month following the last fosaprepitant/aprepitant dose. Risk D: Consider therapy modification

Fosaprepitant: May decrease the serum concentration of Contraceptives (Progestins). The active metabolite aprepitant is likely responsible for this effect. Management: Alternative or additional methods of contraception should be used both during treatment with aprepitant or fosaprepitant and for at least one month following the last aprepitant/fosaprepitant dose. Risk D: Consider therapy modification

Fosphenytoin: May diminish the therapeutic effect of Contraceptives (Estrogens). Contraceptive failure is possible. Management: Use of an alternative, nonhormonal means of contraception is recommended. Risk D: Consider therapy modification

Fosphenytoin: May diminish the therapeutic effect of Contraceptives (Progestins). Contraceptive failure is possible. Management: Contraceptive failure is possible. Use of an alternative, nonhormonal contraceptive is recommended. Risk D: Consider therapy modification

Griseofulvin: May diminish the therapeutic effect of Contraceptives (Progestins). Contraceptive failure is possible. Risk X: Avoid combination

Griseofulvin: May increase the metabolism of Contraceptives (Estrogens). Contraceptive failure is possible. Management: Use an alternative, nonhormonal form of contraception, or use an alternative to griseofulvin. Risk D: Consider therapy modification

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. Risk C: Monitor therapy

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. Risk C: Monitor therapy

Lamotrigine: Contraceptives (Estrogens) may decrease the serum concentration of Lamotrigine. Management: Monitor for increased serum concentrations/effects of lamotrigine in patients in whom a hormonal contraceptive is discontinued/dose decreased (this includes during a pill-free week). A reduced dosage of lamotrigine may be needed. Risk D: Consider therapy modification

Lamotrigine: May decrease the serum concentration of Contraceptives (Progestins). Management: Women using progestin-only "minipill" products may be at risk for contraceptive failure; it is unclear if other progestin-containing products would be significantly impacted. Alternative, non-hormonal, means of contraception are recommended. Risk D: Consider therapy modification

Modafinil: May decrease the serum concentration of Contraceptives (Estrogens). Management: The manufacturer recommends that patients use nonhormonal contraceptives, in addition to or in place of hormonal contraceptives, during and for one month following treatment with modafinil. Risk D: Consider therapy modification

Mycophenolate: May decrease the serum concentration of Contraceptives (Estrogens). Average AUC values were unchanged, but there was evidence of substantial patient-to-patient variability in response to this combination. Management: Women of childbearing potential who are receiving mycophenolate mofetil should consider using an alternative and/or additional form of contraception. Risk D: Consider therapy modification

Mycophenolate: May decrease the serum concentration of Contraceptives (Progestins). Management: Use of an additional or alternative (nonhormonal) method of contraception should be considered. Risk D: Consider therapy modification

Nafcillin: May increase the metabolism of Contraceptives (Estrogens). Management: Use of an alternative, nonhormonal form of contraception during nafcillin therapy is recommended. Risk D: Consider therapy modification

Nevirapine: May decrease the serum concentration of Contraceptives (Estrogens). Risk D: Consider therapy modification

Nevirapine: May decrease the serum concentration of Contraceptives (Progestins). Risk D: Consider therapy modification

OXcarbazepine: May decrease the serum concentration of Contraceptives (Estrogens). Contraceptive failure is possible. Management: Use of an alternative, nonhormonal contraceptive is recommended. Risk D: Consider therapy modification

OXcarbazepine: May decrease the serum concentration of Contraceptives (Progestins). Management: Contraceptive failure is possible. Use of an additional or alternative, nonhormonal method of contraception is recommended. Risk D: Consider therapy modification

Phenytoin: May diminish the therapeutic effect of Contraceptives (Estrogens). Contraceptive failure is possible. Management: Use of an alternative, nonhormonal means of contraception is recommended. Risk D: Consider therapy modification

Phenytoin: May diminish the therapeutic effect of Contraceptives (Progestins). Contraceptive failure is possible. Management: Contraceptive failure is possible. Use of an alternative, nonhormonal contraceptive is recommended. Risk D: Consider therapy modification

Pimozide: CYP3A4 Inhibitors (Weak) may increase the serum concentration of Pimozide. Risk X: Avoid combination

Protease Inhibitors: May decrease the serum concentration of Contraceptives (Estrogens). Management: Use oral contraceptives containing at least 35mcg ethinyl estradiol with atazanavir/ritonavir, or no more than 30mcg in patients receiving atazanavir alone. Use of an alternative, non-hormonal contraceptive is recommended with other protease inhibitors. Exceptions: Indinavir. Risk D: Consider therapy modification

Retinoic Acid Derivatives: May diminish the therapeutic effect of Contraceptives (Progestins). Retinoic Acid Derivatives may decrease the serum concentration of Contraceptives (Progestins). Management: Two forms of effective contraception should be used in patients receiving retinoic acid derivatives. Particularly, microdosed progesterone-only preparations may be inadequately effective. Risk D: Consider therapy modification



Retinoic Acid Derivatives: May diminish the therapeutic effect of Contraceptives (Estrogens). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. Exceptions: Adapalene; Alitretinoin; Tretinoin (Topical). Risk C: Monitor therapy

Rifamycin Derivatives: May decrease the serum concentration of Contraceptives (Estrogens). Contraceptive failure is possible. Management: Use of an alternative, nonhormonal contraceptive is recommended. Risk D: Consider therapy modification

Rifamycin Derivatives: May decrease the serum concentration of Contraceptives (Progestins). Contraceptive failure is possible. Management: Contraceptive failure is possible. Use of an alternative, nonhormonal contraceptive is recommended. Risk D: Consider therapy modification

ROPINI Role: Estrogen Derivatives may increase the serum concentration of ROPINI Role. Risk C: Monitor therapy

Rufinamide: May decrease the serum concentration of Ethinyl Estradiol. Risk D: Consider therapy modification

Rufinamide: May decrease the serum concentration of Norethindrone. Risk D: Consider therapy modification

Selegiline: Contraceptives (Estrogens) may increase the serum concentration of Selegiline. Risk C: Monitor therapy

Selegiline: Contraceptives (Progestins) may increase the serum concentration of Selegiline. Risk C: Monitor therapy

St Johns Wort: May diminish the therapeutic effect of Contraceptives (Estrogens). Contraceptive failure is possible. Management: Consider an alternative to St John's wort if possible. If this combination is used, an alternative, nonhormonal contraceptive is recommended. Risk D: Consider therapy modification

St Johns Wort: May diminish the therapeutic effect of Contraceptives (Progestins). Contraceptive failure is possible. Management: Consider using a product other than St John's wort. Contraceptive failure is possible. Use of an alternative, nonhormonal contraceptive is recommended. Risk D: Consider therapy modification

Telaprevir: May decrease the serum concentration of Contraceptives (Estrogens). Management: Two different nonhormonal forms of contraception are required for women of childbearing potential taking telaprevir. Hormonal contraceptives may be less effective during concurrent telaprevir and for up to 2 weeks after telaprevir discontinuation. Risk D: Consider therapy modification

Telaprevir: May decrease the serum concentration of Contraceptives (Progestins). Management: Two different nonhormonal forms of contraception are required for women of childbearing potential taking telaprevir. Hormonal contraceptives may be less effective during concurrent telaprevir and for up to 2 weeks after telaprevir discontinuation. Risk D: Consider therapy modification

Theophylline Derivatives: Contraceptives (Estrogens) may increase the serum concentration of Theophylline Derivatives. Exceptions: Dyphylline. Risk C: Monitor therapy

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. Risk C: Monitor therapy

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. Management: Women using hormonal contraceptives should consider alternative, non-hormonal forms of contraception. Risk D: Consider therapy modification

TiZANidine: Contraceptives (Estrogens) may increase the serum concentration of TiZANidine. Risk C: Monitor therapy

Tocilizumab: May decrease the serum concentration of CYP3A4 Substrates. Risk C: Monitor therapy

Topiramate: May decrease the serum concentration of Contraceptives (Estrogens). Contraceptive failure is possible. Management: Risk appears greatest for higher topiramate doses (200 mg/day or greater). Some have recommended using at least 50 mcg/day of ethinyl estradiol, but the effectiveness of this is unclear. Consider a nonhormonal form of contraception. Risk D: Consider therapy modification

Topiramate: May decrease the serum concentration of Contraceptives (Progestins). Management: Caution patients that this combination may be associated with reduced contraceptive effectiveness. Consider adding an additional (non-hormonal) contraceptive method. Risk D: Consider therapy modification

Tranexamic Acid: Contraceptives (Progestins) may enhance the thrombogenic effect of Tranexamic Acid. Management: Ensure that the potential benefits of concurrent therapy outweigh the increased risk of potential thrombosis that accompanies use of tranexamic acid with hormonal contraceptives. Risk D: Consider therapy modification

Tranexamic Acid: Contraceptives (Estrogens) may enhance the thrombogenic effect of Tranexamic Acid. Management: Ensure that the potential benefits of concurrent therapy outweigh the increased risk of potential thrombosis that accompanies use of tranexamic acid with hormonal contraceptives. Risk D: Consider therapy modification

Ursodiol: Estrogen Derivatives may diminish the therapeutic effect of Ursodiol. Risk C: Monitor therapy

Vitamin K Antagonists (eg, warfarin): Contraceptives (Estrogens) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. Risk D: Consider therapy modification

Vitamin K Antagonists (eg, warfarin): Contraceptives (Progestins) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. Management: When possible, concomitant hormonal contraceptives and coumarin derivatives should be avoided in order to eliminate the risk of thromboembolic disorders. Consider using an alternative, nonhormonal contraceptive. Risk D: Consider therapy modification

Voriconazole: May decrease the metabolism of Contraceptives (Estrogens). Contraceptives (Estrogens) may increase the serum concentration of Voriconazole. Risk C: Monitor therapy

Voriconazole: May increase the serum concentration of Contraceptives (Progestins). Contraceptives (Progestins) may increase the serum concentration of Voriconazole. Risk C: Monitor therapy

Ethanol/Nutrition/Herb Interactions

Ethanol: Routine use increases estrogen level and risk of breast cancer; avoid ethanol. Ethanol may also increase the risk of osteoporosis.

Food: CNS effects of caffeine may be enhanced if combination hormonal contraceptives are used concurrently with caffeine. Grapefruit juice increases ethinyl estradiol concentrations and would be expected to increase progesterone serum levels as well; clinical implications are unclear. Norethindrone absorption is increased by 27% following administration with food.

Herb/Nutraceutical: St John's wort may decrease levels. Herbs with estrogenic properties may enhance the adverse/toxic effect of estrogen derivatives; examples include alfalfa, black cohosh, bloodroot, hops, kudzu, licorice, red clover, saw palmetto, soybean, thyme, wild yam, yucca. Herbs with progestogenic properties may enhance the adverse/toxic effect of progestins; examples include bloodroot, chasteberry, damiana, oregano, yucca.  
Test Interactions

Increased prothrombin and factors VII, VIII, IX, X; increased platelet aggregability, thyroid-binding globulin, total thyroid hormone (T4), serum triglycerides/phospholipids; decreased antithrombin III, serum folate concentration; pathologist should be advised of estrogen/progesterone therapy when specimens are submitted

Monitoring Parameters

Before starting therapy, a physical exam with reference to the breasts and pelvis are recommended, including a Papanicolaou smear. Exam may be deferred if appropriate; pregnancy should be ruled out prior to use. Monitor patient closely for loss of vision, sudden onset of proptosis, diplopia, migraine; blood pressure; signs and symptoms of thromboembolic disorders; signs or symptoms of depression; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias; thyroid function in patients on thyroid hormone replacement therapy. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding.

Menopausal symptoms: Assess need for therapy at 3- to 6-month intervals

Prevention of osteoporosis: Bone density measurement

Nursing: Physical Assessment/Monitoring

See individual agents.

Monitoring: Lab Tests

Monitor glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias.

Patient Education

See individual agents.

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, oral:

femhrt® 1/5: Ethinyl estradiol 0.005 mg and norethindrone acetate 1 mg (28s, 90s) [white tablets]

femhrt® Lo 0.5/2.5: Ethinyl estradiol 0.0025 mg and norethindrone acetate 0.5 mg (28s, 90s) [white tablets]

Jevantique™ 1/5: Ethinyl estradiol 0.005 mg and norethindrone acetate 1 mg (28s, 90s) [white tablets]

Jinteli™: Ethinyl estradiol 0.005 mg and norethindrone acetate 1 mg (28s, 90s) [white tablets]

Tablet, oral, monophasic formulations:

Balziva™: Ethinyl estradiol 0.035 mg and norethindrone 0.4 mg (28s) [21 light peach tablets and 7 white inactive tablets]

Brevicon®: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg (28s) [21 blue tablets and 7 orange inactive tablets]

Cyclafem™ 1/35: Ethinyl estradiol 0.035 mg and norethindrone 1 mg [21 pink tablets and 7 light green inactive tablets] (28s)

Gildess® FE 1/20: Ethinyl estradiol 0.02 mg and norethindrone acetate 1 mg [21 white tablets] and ferrous fumarate 75 mg [7 white-speckled brown tablets] (28s)

Gildess® FE 1.5/30: Ethinyl estradiol 0.03 mg and norethindrone acetate 1.5 mg [21 light green tablets] and ferrous fumarate 75 mg [7 white-speckled brown tablets] (28s)

Junel® 1/20: Ethinyl estradiol 0.02 mg and norethindrone acetate 1 mg (21s) [yellow tablets]

Junel® 1.5/30: Ethinyl estradiol 0.03 mg and norethindrone acetate 1.5 mg (21s) [pink tablets]

Junel® Fe 1/20: Ethinyl estradiol 0.02 mg and norethindrone acetate 1 mg [21 yellow tablets] and ferrous fumarate 75 mg [7 brown tablets] (28s)

Junel® Fe 1.5/30: Ethinyl estradiol 0.03 mg and norethindrone acetate 1.5 mg [21 pink tablets] and ferrous fumarate 75 mg [7 brown tablets] (28s)

Loestrin® 21 1/20: Ethinyl estradiol 0.02 mg and norethindrone acetate 1 mg (21s) [light yellow tablets]

Loestrin® 21 1.5/30: Ethinyl estradiol 0.03 mg and norethindrone acetate 1.5 mg (21s) [pink tablets]

Lo Loestrin™ Fe: Ethinyl estradiol 0.01 mg and norethindrone acetate 1mg [24 blue tablets] and ethinyl estradiol 0.01 mg [2 white tablets] and ferrous fumarate 75 mg [2 brown tablets] (28s)

Loestrin® 24 Fe: Ethinyl estradiol 0.02 mg and norethindrone acetate 1 mg [24 white tablets] and ferrous fumarate 75 mg [4 brown tablets] (28s)

Loestrin® Fe 1/20: Ethinyl estradiol 0.02 mg and norethindrone acetate 1 mg [21 light yellow tablets] and ferrous fumarate 75 mg [7 brown tablets] (28s)

Loestrin® Fe 1.5/30: Ethinyl estradiol 0.03 mg and norethindrone acetate 1.5 mg [21 pink tablets] and ferrous fumarate 75 mg [7 brown tablets] (28s)

Microgestin® 1/20: Ethinyl estradiol 0.02 mg and norethindrone acetate 1 mg (21s) [white tablets]

Microgestin® 1.5/30: Ethinyl estradiol 0.03 mg and norethindrone acetate 1.5 mg (21s) [green tablets]

Microgestin® Fe 1/20: Ethinyl estradiol 0.02 mg and norethindrone acetate 1 mg [21 white

tablets] and ferrous fumarate 75 mg [7 brown tablets] (28s)

Microgestin® Fe 1.5/30: Ethinyl estradiol 0.03 mg and norethindrone acetate 1.5 mg [21 green tablets] and ferrous fumarate 75 mg [7 brown tablets] (28s)

Modicon®: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg (28s) [21 white tablets and 7 green inactive tablets]

Necon® 0.5/35: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg (28s) [21 light yellow tablets and 7 white inactive tablets]

Necon® 1/35: Ethinyl estradiol 0.035 mg and norethindrone 1 mg (28s) [21 dark yellow tablets and 7 white inactive tablets]

Norinyl® 1+35: Ethinyl estradiol 0.035 mg and norethindrone 1 mg (28s) [21 yellow-green tablets and 7 orange inactive tablets]

Nortrel® 0.5/35: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg (28s) [21 light yellow tablets and 7 white inactive tablets]

Nortrel® 1/35:

Ethinyl estradiol 0.035 mg and norethindrone 1 mg (21s) [yellow tablets]

Ethinyl estradiol 0.035 mg and norethindrone 1 mg (28s) [21 yellow tablets and 7 white inactive tablets]

Ortho-Novum® 1/35: Ethinyl estradiol 0.035 mg and norethindrone 1 mg (28s) [21 peach tablets and 7 green inactive tablets]

Ovcon® 35: Ethinyl estradiol 0.035 mg and norethindrone 0.4 mg (28s) [21 light peach tablets and 7 green inactive tablets]

Ovcon® 50: Ethinyl estradiol 0.05 mg and norethindrone 1 mg (28s) [21 yellow tablets and 7 green inactive tablets]

Zenchant™: Ethinyl estradiol 0.035 mg and norethindrone 0.4 mg (28s) [21 orange tablets and 7 white inactive tablets]

Tablet, chewable, oral, monophasic formulations: Ethinyl estradiol 0.035 mg and norethindrone 0.4 mg [21 tablets] and ferrous fumarate 75 mg [7 tablets] (28s)

Femcon® Fe: Ethinyl estradiol 0.035 mg and norethindrone 0.4 mg [21 white tablets] and ferrous fumarate 75 mg [7 brown tablets] [spearmint flavor] (28s)

Generess™ Fe: Ethinyl estradiol 0.025 mg and norethindrone 0.8 mg [24 light green tablets] and ferrous fumarate 75 mg [4 brown tablets] (28s)

Zenchant Fe™: Ethinyl estradiol 0.035 mg and norethindrone 0.4 mg [21 light yellow tablets] and ferrous fumarate 75 mg [7 brown tablets] [spearmint flavor] (28s)

Zeosa™: Ethinyl estradiol 0.035 mg and norethindrone 0.4 mg [21 light yellow tablets] and ferrous fumarate 75 mg [7 brown tablets] [spearmint flavor] (28s)

Tablet, oral, biphasic formulations:

Necon® 10/11:

Day 1-10: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg [10 light yellow tablets]

Day 11-21: Ethinyl estradiol 0.035 mg and norethindrone 1 mg [11 dark yellow tablets]

Day 22-28: 7 white inactive tablets (28s)

Tablet, oral, triphasic formulations:

Aranelle®:

Day 1-7: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg [7 light yellow tablets]

Day 8-16: Ethinyl estradiol 0.035 mg and norethindrone 1 mg [9 white tablets]

Day 17-21: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg [5 light yellow tablets]

Day 22-28: 7 peach inactive tablets (28s)

Cyclafem™ 7/7/7:

Day 1-7: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg [7 white tablets]

Day 8-14: Ethinyl estradiol 0.035 mg and norethindrone 0.75 mg [7 light pink tablets]

Day 15-21: Ethinyl estradiol 0.035 mg and norethindrone 1 mg [7 pink tablets]

Day 22-28: 7 light green inactive tablets (28s)

Estrostep® Fe:

Day 1-5: Ethinyl estradiol 0.02 mg and norethindrone acetate 1 mg [5 white triangular tablets]

Day 6-12: Ethinyl estradiol 0.03 mg and norethindrone acetate 1 mg [7 white square tablets]

Day 13-21: Ethinyl estradiol 0.035 mg and norethindrone acetate 1 mg [9 white round tablets]

Day 22-28: Ferrous fumarate 75 mg [7 brown tablets] (28s)

Leena®:

Day 1-7: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg [7 light blue tablets]

Day 8-16: Ethinyl estradiol 0.035 mg and norethindrone 1 mg [9 light yellow-green tablets]

Day 17-21: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg [5 light blue tablets]

Day 22-28: 7 orange inactive tablets (28s)

Necon® 7/7/7, Ortho-Novum® 7/7/7:

Day 1-7: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg [7 white tablets]

Day 8-14: Ethinyl estradiol 0.035 mg and norethindrone 0.75 mg [7 light peach tablets]

Day 15-21: Ethinyl estradiol 0.035 mg and norethindrone 1 mg [7 peach tablets]

Day 22-28: 7 green inactive tablets (28s)

Nortrel® 7/7/7:

Day 1-7: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg [7 light yellow tablets]

Day 8-14: Ethinyl estradiol 0.035 mg and norethindrone 0.75 mg [7 blue tablets]

Day 15-21: Ethinyl estradiol 0.035 mg and norethindrone 1 mg [7 peach tablets]

Day 22-28: 7 white inactive tablets (28s)

Tilia™ Fe:

Day 1-5: Ethinyl estradiol 0.02 mg and norethindrone acetate 1 mg [5 white triangular tablets]

Day 6-12: Ethinyl estradiol 0.03 mg and norethindrone acetate 1 mg [7 white square tablets]

Day 13-21: Ethinyl estradiol 0.035 mg and norethindrone acetate 1 mg [9 white round tablets]

Day 22-28: Ferrous fumarate 75 mg [7 brown tablets] (28s)

Tri-Legest™ Fe:

Day 1-5: Ethinyl estradiol 0.02 mg and norethindrone acetate 1 mg [5 light pink tablets]

Day 6-12: Ethinyl estradiol 0.03 mg and norethindrone acetate 1 mg [7 light yellow tablets]

Day 13-21: Ethinyl estradiol 0.035 mg and norethindrone acetate 1 mg [9 light blue tablets]

Day 22-28: Ferrous fumarate 75 mg [7 brown tablets] (28s)

Tri-Norinyl®:

Day 1-7: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg [7 blue tablets]

Day 8-16: Ethinyl estradiol 0.035 mg and norethindrone 1 mg [9 yellow-green tablets]

Day 17-21: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg [5 blue tablets]

Day 22-28: 7 orange inactive tablets (28s)

Generic Available (U.S.)

Yes

Pricing: U.S. ([www.drugstore.com](http://www.drugstore.com))

Chewable (Femcon Fe)

0.4-35 mg-mcg (28): \$85.99

Chewable (Zenchent FE)

0.4-35 mg-mcg (28): \$72.99

Chewable (Zeosa)

0.4-35 mg-mcg (28): \$72.99

Tablets (Aranelle)

0.5/1/0.5-35 mg-mcg (28): \$38.99

Tablets (Balziva)

0.4-35 mg-mcg (28): \$43.99

Tablets (Brevicon (28))

0.5-35 mg-mcg (28): \$71.99

Tablets (Estrostep Fe)

1-20/1-30/1-35 mg-mcg (28): \$98.48

Tablets (Femhrt 1/5)

1-5 mg-mcg (28): \$89.99

1-5 mg-mcg (30): \$82.99

Tablets (Femhrt Low Dose)

0.5-2.5 mg-mcg (28): \$75.99

0.5-2.5 mg-mcg (30): \$80.99

Tablets (Jinteli)

1-5 mg-mcg (28): \$64.99

1-5 mg-mcg (90): \$192.00

Tablets (Junel 1.5/30)

1.5-30 mg-mcg (21): \$29.99

Tablets (Junel 1/20)

1-20 mg-mcg (21): \$29.99

Tablets (Junel FE 1.5/30)

1.5-30 mg-mcg (28): \$29.99

Tablets (Junel FE 1/20)

1-20 mg-mcg (28): \$28.99

Tablets (Lo Loestrin Fe)



1 MG-10 MCG / 10 mcg (28): \$80.99

Tablets (Loestrin 1.5/30 (21))

1.5-30 mg-mcg (21): \$92.99

Tablets (Loestrin 1/20 (21))

1-20 mg-mcg (21): \$92.99

Tablets (Loestrin 24 Fe)

1-20 mg-mcg (28): \$80.99

Tablets (Loestrin Fe 1.5/30)

1.5-30 mg-mcg (28): \$90.99

Tablets (Loestrin Fe 1/20)

1-20 mg-mcg (28): \$90.99

Tablets (Microgestin FE 1.5/30)

1.5-30 mg-mcg (28): \$28.75

Tablets (Modicon (28))

0.5-35 mg-mcg (28): \$59.99

Tablets (Necon 0.5/35 (28))

0.5-35 mg-mcg (28): \$32.99

Tablets (Necon 10/11 (28))

35 mcg (28): \$35.99

Tablets (Norinyl 1+35 (28))

1-35 mg-mcg (28): \$73.99

Tablets (Nortrel 0.5/35 (28))

0.5-35 mg-mcg (28): \$30.99

Tablets (Nortrel 1/35 (28))

1-35 mg-mcg (28): \$27.99

Tablets (Nortrel 7/7/7)

0.5/0.75/1-35 mg-mcg (28): \$30.99

35 mcg (28): \$55.99

Tablets (Ovcon-35 (28))

0.4-35 mg-mcg (28): \$95.31

Tablets (Ovcon-50)

50-1 mcg-mg (28): \$97.99

Tablets (Tilia Fe)

1-20/1-30/1-35 mg-mcg (28): \$48.99

Tablets (Tri-Legest Fe)

1-20/1-30/1-35 mg-mcg (28): \$54.99

Tablets (Tri-Norinyl (28))

0.5/1/0.5-35 mg-mcg (28): \$78.48

Tablets (Zenchent)

0.4-35 mg-mcg (28): \$43.99

Mechanism of Action

Combination oral contraceptives inhibit ovulation via a negative feedback mechanism on the hypothalamus, which alters the normal pattern of gonadotropin secretion of a follicle-stimulating hormone (FSH) and luteinizing hormone by the anterior pituitary. The follicular phase FSH and midcycle surge of gonadotropins are inhibited. In addition, combination hormonal contraceptives produce alterations in the genital tract, including changes in the cervical mucus, rendering it unfavorable for sperm penetration even if ovulation occurs. Changes in the endometrium may also occur, producing an unfavorable environment for nidation. Combination hormonal contraceptive drugs may alter the tubal transport of the ova through the fallopian tubes. Progestational agents may also alter sperm fertility.

In postmenopausal women, exogenous estrogen is used to replace decreased endogenous production. The addition of progestin reduces the incidence of endometrial hyperplasia and risk of endometrial cancer in women with an intact uterus.

Pharmacodynamics/Kinetics

Norethindrone: See individual monograph.

Ethinyl estradiol:

Absorption: Rapid

Bioavailability: 43% to 55%

Distribution: Vd: 2-4 L/kg

Protein binding: >95% to albumin

Metabolism: Hepatic via oxidation and conjugation in GI tract; hydroxylated via CYP3A4 to metabolites; first-pass effect; enterohepatic recirculation; reversibly converted to estrone and estriol

Half-life elimination: 19-24 hours

Excretion: Urine (as estradiol, estrone, and estriol); feces

Pharmacogenomic Genes of Interest

BRCA Genes  
CYP3A4  
Factor V  
Prothrombin

Local Anesthetic/Vasoconstrictor Precautions

No information available to require special precautions

Effects on Dental Treatment

When prescribing antibiotics, patient must be warned to use additional methods of birth control if on oral contraceptives.

Effects on Bleeding

No information available to require special precautions

Related Information

Contraceptive Comparison

Pharmacotherapy Pearls

Once ingested, small amounts of norethindrone acetate are metabolized to ethinyl estradiol, therefore, norethindrone acetate 1 mg is equivalent to the oral administration of ethinyl estradiol 2.8 mcg

Mental Health: Effects on Mental Status

May cause dizziness, headache, depression, insomnia, nervousness, irritability, and mood disturbances

Mental Health: Effects on Psychiatric Treatment

Barbiturates decrease the effects of oral contraceptives; may increase the toxicity of the benzodiazepines and TCAs. The Women's Health Initiative (WHI) Memory Study reported an increased risk of developing dementia in postmenopausal women  $\geq 65$  years of age during 4 years of treatment with oral conjugated equine estrogens and medroxyprogesterone acetate relative to placebo (1.8% vs 0.9%). Relative risk was 2.05 (95% CI 1.21-3.48). Therefore, estrogens and progestins should not be used for the prevention of dementia. The WHI also reported an increased risk of stroke (29 vs 21 per 10,000 women-years) compared to women receiving placebo. The increase in risk was observed after the first year and persisted. May cause hypertriglyceridemia; monitor in patients receiving antipsychotics especially clozapine, olanzapine, and quetiapine.

Cardiovascular Considerations

It is important to recognize that hormone-based contraceptives may induce or worsen hypertension. These problems are less severe with low-dose ones. Furthermore, hormone-based contraceptives may precipitate thromboembolic events, particularly in women who smoke. It is important that patients on these contraceptives long-term undergo monitoring of blood pressure and avoid cigarette use.

Index Terms

Norethindrone Acetate and Ethinyl Estradiol; Ortho Novum

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International Brand Names

Activelle (AR, FI, HK, IL, KP, MY, SE, SG, TH, TW, UY); Brevinor (AU, BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZM, ZW); Brevinor 21 (NZ); Brevinor 28 (AU); Covina (TW); Estracomb (IL); Estragest TTS (IL); Eveclin Half (KP); Eveprem (KP); Eviclin (KP); Evorel Cont (IL); Evorel Conti (AR); Evorel Sequi (IL); Evorelconti (MX); Kliogest (KP, PK, SG); Micropil (PH); Norimin (AE, AU, BF, BH, BJ, CI, CY, EG, ET, GB, GH, GM, GN, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NZ, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZM, ZW); Novofem (EE, HK); Ortho 7 7 7 (BB, BM, BS, BZ, GY, JM, NL, PR, SR, TT); Ortho-Novum 1 35 (CO, FR); Ortho-Novum 1/35 (FR); Ovysmen (AE, BE, BF, BH, BJ, CI, CY, EG, ET, GB, GH, GM, GN, IQ, IR, JO, KE, KW, LB, LR, LY, MA,

ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZM, ZW);  
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GM, GN, IE, IT, KE, LR, MA, ML, MR, MU, MW, NE, NG, PL, RU, SC, SD, SL, SN, TN, TZ, UG,  
ZA, ZM, ZW); Trisekvens (SE); Trisequens (BR, CN, PE, PY, UY); Trisequens Forte (IL)

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