**AVIANE- levonorgestrel and ethinyl estradiol**
**Teva Pharmaceuticals USA, Inc.**

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**Aviane® 28 Tablets**
**(levonorgestrel and ethinyl estradiol tablets USP)**

**Rx only**

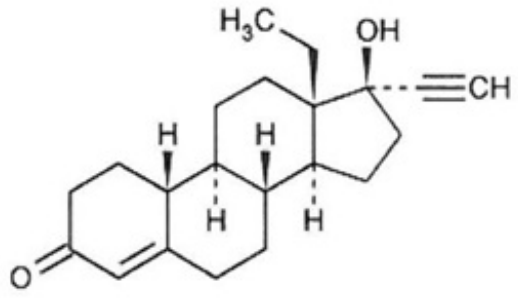
**Patients should be counseled that oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases (STDs) such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.**

## DESCRIPTION

21 orange active tablets each containing 0.10 mg of levonorgestrel, USP (-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one, a totally synthetic progestogen, and 0.02 mg of ethinyl estradiol, USP, (19-Nor-17α -pregna-1,3,5(10)-trien-20-yne-3,17-diol). The inactive ingredients present are: FD&C yellow no. 6 aluminum lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, pregelatinized corn starch, sodium starch glycolate and titanium dioxide.

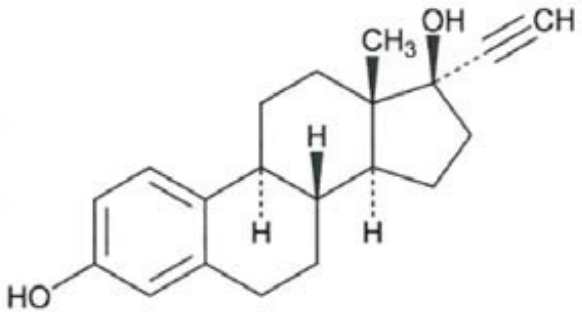
7 light-green, inert tablets each containing: D&C yellow no. 10 aluminum lake, FD&C blue no. 1 aluminum lake, FD&C yellow no. 6 aluminum lake, lactose monohydrate, magnesium stearate, microcrystalline cellulose and pregelatinized corn starch.

Levonorgestrel, USP




$C_{21}H_{28}O_2$ M.W. 312.45

Ethinyl Estradiol, USP




$C_{20}H_{24}O_2$ M.W. 296.40

## CLINICAL PHARMACOLOGY

### Mode of Action

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

### Pharmacokinetics

*Absorption*

No specific investigation of the absolute bioavailability of Aviane in humans has been conducted. However, literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability about 100%) and is not subject to first-pass metabolism. Ethinyl estradiol is rapidly and almost completely absorbed from the gastrointestinal tract but, due to first-pass metabolism in gut mucosa and liver, the bioavailability of ethinyl estradiol is between 38% and 48%.

After a single dose of Aviane to 22 women under fasting conditions, maximum serum concentrations of levonorgestrel are 2.8 ± 0.9 ng/mL (mean ± SD) at 1.6 ± 0.9 hours. At steady state, attained from day 19 onwards, maximum levonorgestrel concentrations of 6.0 ± 2.7 ng/mL are reached at 1.5 ± 0.5 hours after the daily dose. The minimum serum levels of levonorgestrel at steady state are 1.9 ± 1.0 ng/mL. Observed levonorgestrel concentrations increased from day 1 (single dose) to days 6 and 21 (multiple doses) by 34% and 96%, respectively (**Figure I**). Unbound levonorgestrel concentrations increased from day 1 to days 6 and 21 by 25% and 83%, respectively. The kinetics of total levonorgestrel are nonlinear due to an increase in binding of levonorgestrel to sex hormone binding globulin (SHBG), which is attributed to increased SHBG levels that are induced by the daily administration of ethinyl estradiol.

Following a single dose, maximum serum concentrations of ethinyl estradiol of 62 ± 21 pg/mL are reached at 1.5 ± 0.5 hours. At steady state, attained from at least day 6 onwards, maximum concentrations of ethinyl estradiol were 77 ± 30 pg/mL and were reached at 1.3 ± 0.7 hours after the daily dose. The minimum serum levels of ethinyl estradiol at steady state are 10.5 ± 5.1 pg/mL. Ethinyl estradiol concentrations did not increase from days 1 to 6, but did increase by 19% from days 1 to 21 (**Figure I**).

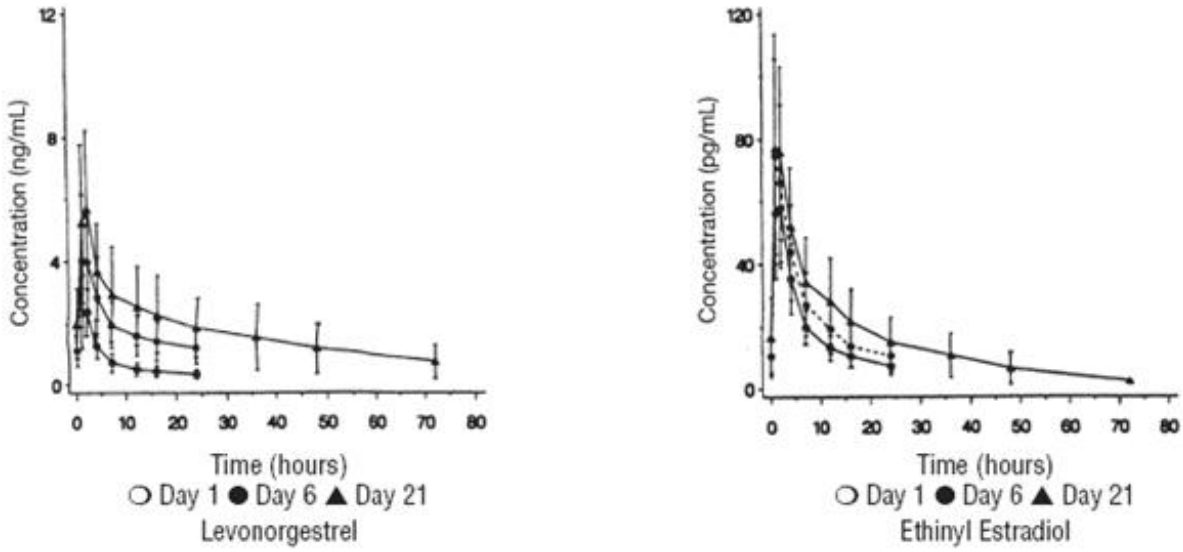



**Figure I: Mean (SE) Levonorgestrel and Ethinyl Estradiol Serum Concentrations in 22 Subjects Receiving 100 mcg Levonorgestrel and 20 mcg Ethinyl Estradiol**

**TABLE I** provides a summary of levonorgestrel and ethinyl estradiol pharmacokinetic parameters.

**TABLE I: MEAN (SD) PHARMACOKINETIC PARAMETERS OF AVIANE OVER A 21 DAY DOSING PERIOD**

| | | | Levonorgestrel | | | |
|---|---|---|---|---|---|---|
| | $C_{max}$ | $T_{max}$ | AUC | CL/F | Vλz/F | SHBG |
| Day | ng/mL | h | ng•h/mL | mL/h/kg | L/kg | nmol/L |
| 1 | 2.75 (0.88) | 1.6 (0.9) | 35.2 (12.8) | 53.7 (20.8) | 2.66 (1.09) | 57 (18) |
| 6 | 4.52 (1.79) | 1.5 (0.7) | 46.0 (18.8) | 40.8 (14.5) | 2.05 (0.86) | 81 (25) |
| 21 | 6.00 (2.65) | 1.5 (0.5) | 68.3 (32.5) | 28.4 (10.3) | 1.43 (0.62) | 93 (40) |
| | | | Unbound Levonorgestrel | | | |
| | pg/mL | h | pg•h/mL | L/h/kg | L/kg | fu% |
| 1 | 51.2 (12.9) | 1.6 (0.9) | 654 (201) | 2.79 (0.97) | 135.9 (41.8) | 1.92 (0.30) |
| 6 | 77.9 (22.0) | 1.5 (0.7) | 794 (240) | 2.24 (0.59) | 112.4 (40.5) | 1.80 (0.24) |
| 21 | 103.6 (36.9) | 1.5 (0.5) | 1177 (452) | 1.57 (0.49) | 78.6 (29.7) | 1.78 (0.19) |
| | | | Ethinyl Estradiol | | | |
| | pg/mL | h | pg•h/mL | mL/h/kg | L/kg | |
| 1 | 62.0 (20.5) | 1.5 (0.5) | 653 (227) | 567 (204) | 14.3 (3.7) | |
| 6 | 76.7 (29.9) | 1.3 (0.7) | 604 (231) | 610 (196) | 15.5 (4.0) | |
| 21 | 82.3 (33.2) | 1.4 (0.6) | 776 (308) | 486 (179) | 12.4 (4.1) | |

*Distribution*

Levonorgestrel in serum is primarily bound to SHBG. Ethinyl estradiol is about 97% bound to plasma albumin. Ethinyl estradiol does not bind to SHBG, but induces SHBG synthesis.

*Metabolism*

*Levonorgestrel*

The most important metabolic pathway occurs in the reduction of the Δ4-3-oxo group and hydroxylation at positions 2α, 1β, and 16β, followed by conjugation. Most of the metabolites that circulate in the blood

are sulfates of 3α,5β-tetrahydro-levonorgestrel, while excretion occurs predominantly in the form of glucuronides. Some of the parent levonorgestrel also circulates as 17β-sulfate. Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for the wide variation observed in levonorgestrel concentrations among users.

*Ethinyl Estradiol*

Cytochrome P450 enzymes (CYP3A4) in the liver are responsible for the 2-hydroxylation that is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion. Levels of Cytochrome P450 (CYP3A) vary widely among individuals and can explain the variation in rates of ethinyl estradiol 2-hydroxylation. Ethinyl estradiol is excreted in the urine and feces as glucuronide and sulfate conjugates, and undergoes enterohepatic circulation.

*Excretion*

The elimination half-life for levonorgestrel is approximately 36 ± 13 hours at steady state. Levonorgestrel and its metabolites are primarily excreted in the urine (40% to 68%) and about 16% to 48% are excreted in feces. The elimination half-life of ethinyl estradiol is 18 ± 4.7 hours at steady state.

**Special Populations**

*Race*

Based on the pharmacokinetic study with Aviane, there are no apparent differences in pharmacokinetic parameters among women of different races.

*Hepatic Insufficiency*

No formal studies have evaluated the effect of hepatic disease on the disposition of Aviane. However, steroid hormones may be poorly metabolized in patients with impaired liver function.

*Renal Insufficiency*

No formal studies have evaluated the effect of renal disease on the disposition of Aviane.

**Drug-Drug Interactions**

See **PRECAUTIONS** section - **Drug Interactions**

## INDICATIONS AND USAGE

Aviane (levonorgestrel and ethinyl estradiol tablets) is indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

Oral contraceptives are highly effective. **TABLE II** lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization, the IUD, and Norplant® System, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

**TABLE II: PERCENTAGE OF WOMEN EXPERIENCING AN UNINTENDED PREGNANCY DURING THE FIRST YEAR OF TYPICAL USE AND THE FIRST YEAR OF PERFECT USE OF CONTRACEPTION AND THE PERCENTAGE CONTINUING USE AT THE END OF THE FIRST YEAR. UNITED STATES.**

| | % of Women Experiencing an Unintended Pregnancy within the | % of Women Continuing Use at One Year [3] |
|---|---|---|

| | First Year of Use | | |
|---|---|---|---|
| Method<br>(1) | Typical Use [1]<br>(2) | Perfect Use [2]<br>(3) | (4) |
| Chance [4] | 85 | 85 | |
| Spermicides [5] | 26 | 6 | 40 |
| Periodic abstinence | 25 | | 63 |
| Calendar | | 9 | |
| Ovulation Method | | 3 | |
| Sympto-Thermal [6] | | 2 | |
| Post-Ovulation | | 1 | |
| Cap [7] | | | |
| Parous Women | 40 | 26 | 42 |
| Nulliparous Women | 20 | 9 | 56 |
| Sponge | | | |
| Parous Women | 40 | 20 | 42 |
| Nulliparous Women | 20 | 9 | 56 |
| Diaphragm [7] | 20 | 6 | 56 |
| Withdrawal | 19 | 4 | |
| Condom [8] | | | |
| Female (Reality) | 21 | 5 | 56 |
| Male | 14 | 3 | 61 |
| Pill | 5 | | 71 |
| Progestin only | | 0.5 | |
| Combined | | 0.1 | |
| IUD | | | |
| Progesterone T | 2.0 | 1.5 | 81 |
| Copper T380A | 0.8 | 0.6 | 78 |
| LNg 20 | 0.1 | 0.1 | 81 |
| Depo-Provera® | 0.3 | 0.3 | 70 |
| Levonorgestrel Implants (Norplant®) | 0.05 | 0.05 | 88 |
| Female Sterilization | 0.5 | 0.5 | 100 |
| Male Sterilization | 0.15 | 0.10 | 100 |
| Emergency Contraceptive Pills: The FDA has concluded that certain combined oral contraceptives containing ethinyl estradiol and norgestrel or levonorgestrel are safe and effective for use as postcoital emergency contraception. Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.[9] | | | |
| Lactation Amenorrhea Method: LAM is a highly effective, temporary method of contraception.[10] | | | |

Source: Trussell J. Contraceptive efficacy. In: Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Kowel D, Guest F. Contraceptive Technology: Seventeenth Revised Edition. New York, NY: Irvington Publishers; 1998.

1. Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
2. Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
3. Among couples attempting to avoid pregnancy, the percentage who continue to use a method for one

year.

4. The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within one year. This estimate was lowered slightly (to 85%) to represent the percent who would become pregnant within one year among women now relying on reversible methods of contraception if they abandoned contraception altogether.
5. Foams, creams, gels, vaginal suppositories, and vaginal film.
6. Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.
7. With spermicidal cream or jelly.
8. Without spermicides.
9. The treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The FDA has declared the following dosage regimens of oral contraceptives to be safe and effective for emergency contraception: for tablets containing 50 mcg of ethinyl estradiol and 500 mcg of norgestrel 1 dose is 2 tablets; for tablets containing 20 mcg of ethinyl estradiol and 100 mcg of levonorgestrel 1 dose is 5 tablets; for tablets containing 30 mcg of ethinyl estradiol and 150 mcg of levonorgestrel 1 dose is 4 tablets.
10. However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

In a clinical trial with Aviane (levonorgestrel and ethinyl estradiol tablets), 1,477 subjects had 7,720 cycles of use and a total of 5 pregnancies were reported. This represents an overall pregnancy rate of 0.84 per 100 woman-years. This rate includes patients who did not take the drug correctly. One or more pills were missed during 1,479 (18.8%) of the 7,870 cycles; thus all tablets were taken during 6,391 (81.2%) of the 7,870 cycles. Of the total 7,870 cycles, a total of 150 cycles were excluded from the calculation of the Pearl index due to the use of backup contraception and/or missing 3 or more consecutive pills.

## CONTRAINDICATIONS

Combination oral contraceptives should not be used in women with any of the following conditions:

- Thrombophlebitis or thromboembolic disorders
- A history of deep-vein thrombophlebitis or thromboembolic disorders
- Cerebrovascular or coronary artery disease (current or past history)
- Valvular heart disease with thrombogenic complications
- Thrombogenic rhythm disorders
- Hereditary or acquired thrombophilias
- Major surgery with prolonged immobilization
- Diabetes with vascular involvement
- Headaches with focal neurological symptoms
- Uncontrolled hypertension
- Known or suspected carcinoma of the breast or personal history of breast cancer
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior pill use
- Hepatic adenomas or carcinomas, or active liver disease
- Known or suspected pregnancy
- Hypersensitivity to any of the components of Aviane

Women who are receiving Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir,

with or without dasabuvir, due to the potential for alanine aminotransferase (ALT) elevations (see WARNINGS, **Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment)**.

## WARNINGS

**Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with the extent of smoking (in epidemiologic studies, 15 or more cigarettes per day was associated with a significantly increased risk) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.**

The use of oral contraceptives is associated with increased risks of several serious conditions including venous and arterial thrombotic and thromboembolic events (such as myocardial infarction, thromboembolism, and stroke), hepatic neoplasia, gallbladder disease, and hypertension, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as certain inherited or acquired thrombophilias, hypertension, hyperlipidemias, obesity, diabetes, and surgery or trauma with increased risk of thrombosis (see **CONTRAINDICATIONS**).

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with higher doses of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower doses of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of disease, namely, a ratio of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the difference in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population. For further information, the reader is referred to a text on epidemiological methods.

### 1. Thromboembolic Disorders and Other Vascular Problems

*a. Myocardial Infarction*

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary-artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six. The risk is very low under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarction in women in their mid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and nonsmokers over the age of 40 (**Figure II**) among women who use oral contraceptives.

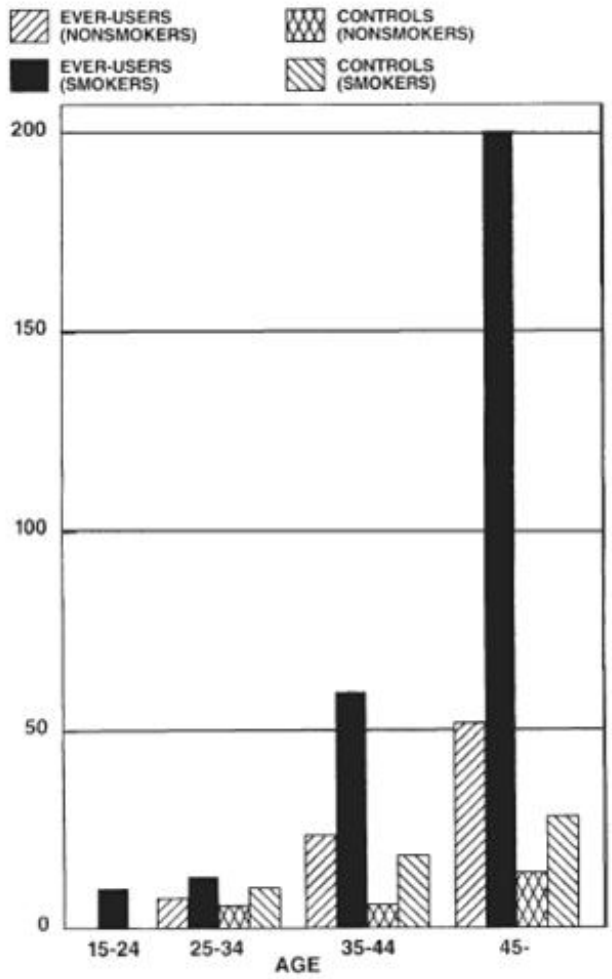



**Figure II: Circulatory Disease Mortality Rates Per 100,000 Woman Years by Age, Smoking Status and Oral Contraceptive Use (Adapted from P.M. Layde and V. Beral, Lancet, 1:541–546, 1981.)**

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age, and obesity. In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see section 10 in **WARNINGS**). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

*b. Venous Thrombosis and Thromboembolism*

An increased risk of venous thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep-vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The approximate incidence of deep-vein thrombosis and pulmonary embolism in users of low dose (< 50 mcg ethinyl estradiol) combination oral contraceptives is up to 4 per 10,000 woman-years compared to 0.5 to 3 per 10,000 woman-years for nonusers. However, the incidence is less than that associated with pregnancy (6 per 10,000 woman-years). The excess risk is highest during the first year a woman ever uses a combined oral contraceptive. Venous thromboembolism may be fatal. The risk of thromboembolic disease due to oral contraceptives is not related to length of use and gradually disappears after pill use is stopped.

A two- to four-fold increase in relative risk of postoperative thromboembolic complications has been

reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four weeks after delivery in women who elect not to breastfeed or after a midtrimester pregnancy termination.

*c. Cerebrovascular Diseases*

Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (> 35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes.

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for nonsmokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension. The attributable risk is also greater in older women. Oral contraceptives also increase the risk for stroke in women with other underlying risk factors such as certain inherited or acquired thrombophilias. Women with migraine (particularly migraine/headaches with focal neurological symptoms, see **CONTRAINDICATIONS**) who take combination oral contraceptives may be at an increased risk of stroke.

*d. Dose-Related Risk of Vascular Disease from Oral Contraceptives*

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents. A decline in serum high-density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogen used in the contraceptive. The amount of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing the lowest estrogen content which is judged appropriate for the individual patient.

*e. Persistence of Risk of Vascular Disease*

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40 to 49 years who had used oral contraceptives for five or more years, but this increased risk was not demonstrated in other age groups.

In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. However, both studies were performed with oral contraceptive formulations containing 50 mcg or higher of estrogens.

**2. Estimates of Mortality from Contraceptive Use**

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (**TABLE III**). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is less than that associated with childbirth. The observation of a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970's — but not reported until 1983. However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral contraceptive use to women who do not have the various risk factors listed in this labeling.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy nonsmoking women (even with the newer low-dose formulations), there are greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception.

Therefore, the Committee recommended that the benefits of oral contraceptive use by healthy nonsmoking women over 40 may outweigh the possible risks. Of course, older women, as all women who take oral contraceptives, should take the lowest possible dose formulation that is effective.

**TABLE III: ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NONSTERILE WOMEN, BY FERTILITY CONTROL METHOD AND ACCORDING TO AGE**

| Method of control and outcome | 15 to 19 | 20 to 24 | 25 to 29 | 30 to 34 | 35 to 39 | 40 to 44 |
|---|---|---|---|---|---|---|
| No fertility control methods * | 7.0 | 7.4 | 9.1 | 14.8 | 25.7 | 28.2 |
| Oral contraceptives nonsmoker ** | 0.3 | 0.5 | 0.9 | 1.9 | 13.8 | 31.6 |
| Oral contraceptives smoker ** | 2.2 | 3.4 | 6.6 | 13.5 | 51.1 | 117.2 |
| IUD ** | 0.8 | 0.8 | 1.0 | 1.0 | 1.4 | 1.4 |
| Condom * | 1.1 | 1.6 | 0.7 | 0.2 | 0.3 | 0.4 |
| Diaphragm/spermicide * | 1.9 | 1.2 | 1.2 | 1.3 | 2.2 | 2.8 |
| Periodic abstinence * | 2.5 | 1.6 | 1.6 | 1.7 | 2.9 | 3.6 |

* Deaths are birth related

** Deaths are method related

Adapted from H.W. Ory, Family Planning Perspectives, *15*:57-63, 1983.

### 3. Carcinoma of the Reproductive Organs and Breasts

Numerous epidemiological studies have examined the association between the use of oral contraceptives and the incidence of breast and cervical cancer.

The risk of having breast cancer diagnosed may be slightly increased among current and recent users of combination oral contraceptives. However, this excess risk appears to decrease over time after combination oral contraceptive discontinuation and by 10 years after cessation the increased risk disappears. Some studies report an increased risk with duration of use while other studies do not and no consistent relationships have been found with dose or type of steroid. Some studies have reported a

small increase in risk for women who first use combination oral contraceptives at a younger age. Most studies show a similar pattern of risk with combination oral contraceptive use regardless of a woman's reproductive history or her family breast cancer history.

Breast cancers diagnosed in current or previous OC users tend to be less clinically advanced than in nonusers.

Women with known or suspected carcinoma of the breast or personal history of breast cancer should not use oral contraceptives because breast cancer is usually a hormonally-sensitive tumor.

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

In spite of many studies of the relationship between combination oral contraceptive use and breast and cervical cancers, a cause-and-effect relationship has not been established.

**4. Hepatic Neoplasia**

Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of these benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use. Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (> 8 years) oral contraceptive users. However, these cancers are extremely rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users.

**5. Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment**

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

**6. Ocular Lesions**

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives that may lead to partial or complete loss of vision. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

**7. Oral Contraceptive Use Before or During Early Pregnancy**

Extensive epidemiological studies have revealed no increased risk of birth defects in infants born to women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy (see **CONTRAINDICATIONS** section).

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

It is recommended that for any patient who has missed two consecutive periods, pregnancy should be

ruled out. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued if pregnancy is confirmed.

**8. Gallbladder Disease**

Combination oral contraceptives may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women. Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

**9. Carbohydrate and Lipid Metabolic Effects**

Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users. Oral contraceptives containing greater than 75 mcg of estrogens cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the nondiabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see **WARNINGS**, **1***a.* and **1***d.*; **PRECAUTIONS**, **3**), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

**10. Elevated Blood Pressure**

An increase in blood pressure has been reported in women taking oral contraceptives and this increase is more likely in older oral contraceptive users and with continued use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing quantities of progestogens.

Women with a history of hypertension or hypertension-related diseases, or renal disease should be encouraged to use another method of contraception. If women with hypertension elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued (see **CONTRAINDICATIONS** section). For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension among ever- and never-users.

**11. Headache**

The onset or exacerbation of migraine or development of headache with a new pattern that is recurrent, persistent, or severe requires discontinuation of oral contraceptives and evaluation of the cause (see **WARNINGS**, **1***c.* and **CONTRAINDICATIONS**).

**12. Bleeding Irregularities**

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. The type and dose of progestogen may be important. If bleeding persists or recurs, nonhormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea (possibly with anovulation),

especially when such a condition was preexistent.

### 13. Ectopic Pregnancy

Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

## PRECAUTIONS

### 1. General

**Patients should be counseled that oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases (STDs) such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.**

### 2. Physical Examination and Follow-Up

A periodic personal and family medical history and complete physical examination are appropriate for all women, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent, or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

### 3. Lipid Disorders

Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult (see WARNINGS, 1a, 1d, and 9).

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

### 4. Liver Function

If jaundice develops in any woman receiving such drugs, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

### 5. Fluid Retention

Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

### 6. Emotional Disorders

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

### 7. Contact Lenses

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

**8. Gastrointestinal**

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

**9. Drug Interactions**

*Concomitant Use with HCV Combination Therapy - Liver Enzyme Elevation*

Do not co-administer Aviane with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations (see **WARNINGS, Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment**).

*Changes in Contraceptive Effectiveness Associated with Coadministration of Other Products*

Contraceptive effectiveness may be reduced when hormonal contraceptives are coadministered with antibiotics, anticonvulsants, and other drugs that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include rifampin, rifabutin, barbiturates, primidone, phenylbutazone, phenytoin, dexamethasone, carbamazepine, felbamate, oxcarbazepine, topiramate, griseofulvin, and modafinil. In such cases a backup nonhormonal method of birth control should be considered.

Several cases of contraceptive failure and breakthrough bleeding have been reported in the literature with concomitant administration of antibiotics such as ampicillin and other penicillins, and tetracyclines. However, clinical pharmacology studies investigating drug interactions between combined oral contraceptives and these antibiotics have reported inconsistent results.

Several of the anti-HIV protease inhibitors have been studied with coadministration of oral combination hormonal contraceptives; significant changes (increase and decrease) in the plasma levels of the estrogen and progestin have been noted in some cases. The safety and efficacy of oral contraceptive products may be affected with coadministration of anti-HIV protease inhibitors. Healthcare providers should refer to the label of the individual anti-HIV protease inhibitors for further drug-drug interaction information.

Herbal products containing St. John's Wort (Hypericum perforatum) may induce hepatic enzymes (cytochrome P 450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

*Increase in Plasma Levels Associated with Coadministered Drugs*

Coadministration of atorvastatin and certain oral contraceptives containing ethinyl estradiol increases AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen increase the bioavailability of ethinyl estradiol since these drugs act as competitive inhibitors for sulfation of ethinyl estradiol in the gastrointestinal wall, a known pathway of elimination for ethinyl estradiol. CYP 3A4 inhibitors such as indinavir, itraconazole, ketoconazole, fluconazole, and troleandomycin may increase plasma hormone levels. Troleandomycin may also increase the risk of intrahepatic cholestasis during coadministration with combination oral contraceptives.

*Changes in Plasma Levels of Coadministered Drugs*

Combination hormonal contraceptives containing some synthetic estrogens (e.g., ethinyl estradiol) may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporin, prednisolone and other corticosteroids, and theophylline have been reported with concomitant administration of oral contraceptives. Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine, and clofibric acid, due to induction of conjugation (particularly glucuronidation), have been noted when these drugs were administered with oral contraceptives.

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

### 10. Interactions with Laboratory Tests

Certain endocrine- and liver-function tests and blood components may be affected by oral contraceptives:

a. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
b. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), $T_4$ by column or by radioimmunoassay. Free $T_3$ resin uptake is decreased, reflecting the elevated TBG; free $T_4$ concentration is unaltered.
c. Other binding proteins may be elevated in serum i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulins (SHBG) leading to increased levels of total circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged.
d. Triglycerides may be increased and levels of various other lipids and lipoproteins may be affected.
e. Glucose tolerance may be decreased.
f. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

### 11. Carcinogenesis

See **WARNINGS** section.

### 12. Pregnancy

*Pregnancy Category X*

See **CONTRAINDICATIONS** and **WARNINGS** sections.

### 13. Nursing Mothers

Small amounts of oral contraceptive steroids and/or metabolites have been identified in the milk of nursing mothers, and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, combination oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use combination oral contraceptives but to use other forms of contraception until she has completely weaned her child.

### 14. Pediatric Use

Safety and efficacy of Aviane tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of Aviane before menarche is not indicated.

### 15. Geriatric Use

Aviane has not been studied in women over 65 years of age and is not indicated in this population.

### 16. Information for the Patient

See Patient Labeling printed below.

## ADVERSE REACTIONS

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

Thromboembolic and thrombotic disorders and other vascular problems (including thrombophlebitis and venous thrombosis with or without pulmonary embolism, mesenteric thrombosis, arterial thromboembolism, myocardial infarction, cerebral hemorrhage, cerebral thrombosis), carcinoma of the

reproductive organs and breasts, hepatic neoplasia (including hepatic adenomas or benign liver tumors), ocular lesions (including retinal vascular thrombosis), gallbladder disease, carbohydrate and lipid effects, elevated blood pressure, and headache including migraine.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related (alphabetically listed):

- Acne
- Amenorrhea
- Anaphylactic/anaphylactoid reactions, including urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms
- Breast changes: tenderness, pain, enlargement, secretion
- Budd-Chiari syndrome
- Cervical erosion and secretion, change in
- Cholestatic jaundice
- Chorea, exacerbation of
- Colitis
- Contact lenses, intolerance to
- Corneal curvature (steepening), change in
- Dizziness
- Edema/fluid retention
- Erythema multiforme
- Erythema nodosum
- Gastrointestinal symptoms (such as abdominal pain, cramps, and bloating)
- Hirsutism
- Infertility after discontinuation of treatment, temporary
- Lactation, diminution in, when given immediately postpartum
- Libido, change in
- Melasma/chloasma which may persist
- Menstrual flow, change in
- Mood changes, including depression
- Nausea
- Nervousness
- Pancreatitis
- Porphyria, exacerbation of
- Rash (allergic)
- Scalp hair, loss of
- Serum folate levels, decrease in
- Spotting
- Systemic lupus erythematosus, exacerbation of
- Unscheduled bleeding
- Vaginitis, including candidiasis
- Varicose veins, aggravation of
- Vomiting
- Weight or appetite (increase or decrease), change in

The following adverse reactions have been reported in users of oral contraceptives:

- Cataracts
- Cystitis-like syndrome
- Dysmenorrhea
- Hemolytic uremic syndrome
- Hemorrhagic eruption

- Optic neuritis, which may lead to partial or complete loss of vision
- Premenstrual syndrome
- Renal function, impaired

## OVERDOSAGE

Symptoms of oral contraceptive overdosage in adults and children may include nausea, vomiting, and drowsiness/fatigue; withdrawal bleeding may occur in females. There is no specific antidote and further treatment of overdose, if necessary, is directed to the symptoms.

## NONCONTRACEPTIVE HEALTH BENEFITS

The following noncontraceptive health benefits related to the use of oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg of mestranol.

Effects on menses:
- Increased menstrual cycle regularity
- Decreased blood loss and decreased incidence of iron deficiency anemia
- Decreased incidence of dysmenorrhea

Effects related to inhibition of ovulation:
- Decreased incidence of functional ovarian cysts
- Decreased incidence of ectopic pregnancies

Effects from long-term use:
- Decreased incidence of fibroadenomas and fibrocystic disease of the breast
- Decreased incidence of acute pelvic inflammatory disease
- Decreased incidence of endometrial cancer
- Decreased incidence of ovarian cancer

## DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, Aviane (levonorgestrel and ethinyl estradiol tablets) must be taken exactly as directed and at intervals not exceeding 24 hours. The dosage of Aviane - 28 is one orange tablet daily for 21 consecutive days, followed by one light-green inert tablet daily for 7 consecutive days, according to the prescribed schedule. It is recommended that Aviane - 28 tablets be taken at the same time each day.

The dispenser should be kept in the wallet supplied to avoid possible fading of the pills. If the pills fade, patients should continue to take them as directed.

### During The First Cycle Of Use

The possibility of ovulation and conception prior to initiation of medication should be considered. The patient should be instructed to begin taking Aviane on either the first Sunday after the onset of menstruation (Sunday Start) or on Day 1 of menstruation (Day 1 Start).

### Sunday Start:

The patient is instructed to begin taking Aviane - 28 on the first Sunday after the onset of menstruation. If menstruation begins on a Sunday, the first tablet (orange) is taken that day. One orange tablet should be taken daily for 21 consecutive days, followed by one light-green inert tablet daily for 7 consecutive days. Withdrawal bleeding should usually occur within 3 days following discontinuation of orange tablets and may not have finished before the next pack is started. During the first cycle, contraceptive

reliance should not be placed on Aviane - 28 until an orange tablet has been taken daily for 7 consecutive days, and a nonhormonal backup method of birth control should be used during those 7 days.

**Day 1 Start:**

During the first cycle of medication, the patient is instructed to begin taking Aviane - 28 during the first 24 hours of her period (day one of her menstrual cycle). One orange tablet should be taken daily for 21 consecutive days, followed by one light-green inert tablet daily for 7 consecutive days. Withdrawal bleeding should usually occur within 3 days following discontinuation of orange tablets and may not have finished before the next pack is started. If medication is begun on day one of the menstrual cycle, no backup contraception is necessary. If Aviane - 28 tablets are started later than day one of the first menstrual cycle or postpartum, contraceptive reliance should not be placed on Aviane - 28 tablets until after the first 7 consecutive days of administration, and a nonhormonal backup method of birth control should be used during those 7 days.

**After the First Cycle of Use**

The patient begins her next and all subsequent courses of tablets on the day after taking her last light-green tablet. She should follow the same dosing schedule: 21 days on orange tablets followed by 7 days on light-green tablets. If in any cycle the patient starts tablets later than the proper day, she should protect herself against pregnancy by using a nonhormonal backup method of birth control until she has taken an orange tablet daily for 7 consecutive days.

**Switching from Another Hormonal Method of Contraception**

When the patient is switching from a 21 day regimen of tablets, she should wait 7 days after her last tablet before she starts Aviane. She will probably experience withdrawal bleeding during that week. She should be sure that no more than 7 days pass after her previous 21 day regimen. When the patient is switching from a 28 day regimen of tablets, she should start her first pack of Aviane on the day after her last tablet. She should not wait any days between packs. The patient may switch any day from a progestin-only pill and should begin Aviane the next day. If switching from an implant or injection, the patient should start Aviane on the day of implant removal or, if using an injection, the day the next injection would be due. In switching from a progestin-only pill, injection, or implant, the patient should be advised to use a nonhormonal backup method of birth control for the first 7 days of tablet taking.

**If Spotting or Breakthrough Bleeding Occurs**

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

**Risk of Pregnancy if Tablets are Missed**

While there is little likelihood of ovulation occurring if only one or two orange tablets are missed, the possibility of ovulation increases with each successive day that scheduled orange tablets are missed. Although the occurrence of pregnancy is unlikely if Aviane is taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed schedule (missed one or more tablets or started taking them on a day later than she should have), the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out.

The risk of pregnancy increases with each active (orange) tablet missed. For additional patient instructions regarding missed tablets, see the **WHAT TO DO IF YOU MISS PILLS** section in the **DETAILED PATIENT LABELING** below.

**Use After Pregnancy, Abortion or Miscarriage**

Aviane may be initiated no earlier than day 28 postpartum in the nonlactating mother or after a second trimester abortion due to the increased risk for thromboembolism (see **CONTRAINDICATIONS**, **WARNINGS**, and **PRECAUTIONS** concerning thromboembolic disease). The patient should be advised to use a nonhormonal backup method for the first 7 days of tablet taking.

Aviane may be initiated immediately after a first trimester abortion or miscarriage. If the patient starts Aviane immediately, backup contraception is not needed.

## HOW SUPPLIED

Aviane® (levonorgestrel and ethinyl estradiol tablets USP), 0.10 mg/0.02 mg is available as 28 tablets packaged in cartons (NDC: 0555-9045-58) of six blister card dispensers. Each blister card dispenser contains 21 orange active tablets and 7 light-green inert tablets. Each orange tablet is round, film coated and debossed with **dp** on one side and **016** on the other side. Each light-green tablet is round and debossed with **dp** on one side and **519** on the other side.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

REFERENCES AVAILABLE UPON REQUEST.

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**Teva Pharmaceuticals USA, Inc.**

North Wales, PA 19454

Rev. C 6/2020

**Aviane® 28 Tablets**
**(levonorgestrel and ethinyl estradiol tablets)**
**BRIEF SUMMARY PATIENT PACKAGE INSERT**

**This product (like all oral contraceptives) is intended to prevent pregnancy. Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases (STDs) such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.**

Oral contraceptives, also known as “birth control pills” or “the pill,” are taken to prevent pregnancy, and when taken correctly, have a failure rate of approximately 1.0% per year (1 pregnancy per 100 women per year of use) when used without missing any pills. The average failure rate of large numbers of pill users is approximately 5% per year (5 pregnancies per 100 women per year of use) when women who miss pills are included. For most women oral contraceptives are also free of serious or unpleasant side effects. However, forgetting to take pills considerably increases the chances of pregnancy.

For the majority of women, oral contraceptives can be taken safely. But there are some women who are at high risk of developing certain serious diseases that can be life-threatening or may cause temporary or permanent disability or death. The risks associated with taking oral contraceptives increase significantly if you:

- smoke
- have high blood pressure, diabetes, high cholesterol, or a tendency to form blood clots
- have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer of the breast or sex organs, jaundice, malignant or benign liver tumors, or major surgery with prolonged immobilization
- have headaches with neurological symptoms

You should not take the pill if you take any Hepatitis C drug combination containing

ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. This may increase levels of the liver enzyme “alanine aminotransferase” (ALT) in the blood.

You should not take the pill if you suspect you are pregnant or have unexplained vaginal bleeding.

Although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy, nonsmoking women, there are also greater potential health risks associated with pregnancy in older women.

**Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral contraceptive use. This risk increases with age and with the amount of smoking (15 or more cigarettes per day has been associated with a significantly increased risk) and is quite marked in women over 35 years of age. Women who use oral contraceptives should not smoke.**

Most side effects of the pill are not serious. The most common such effects are nausea, vomiting, bleeding between menstrual periods, weight gain, breast tenderness, and difficulty wearing contact lenses. These side effects, especially nausea and vomiting, may subside within the first three months of use.

The serious side effects of the pill occur very infrequently, especially if you are in good health and do not smoke. However, you should know that the following medical conditions have been associated with or made worse by the pill:

1. Blood clots in the legs (thrombophlebitis) and lungs (pulmonary embolism), blockage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack and angina pectoris) or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences. Women with migraine also may be at increased risk of stroke with pill use.
2. Liver tumors, which may rupture and cause severe bleeding. A possible but not definite association has been found with the pill and liver cancer. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.
3. High blood pressure, although blood pressure usually returns to normal when the pill is stopped.

The symptoms associated with these serious side effects are discussed in the detailed leaflet given to you with your supply of pills. Notify your healthcare provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anticonvulsants and some antibiotics, herbal preparations containing St. John's Wort (Hypericum perforatum), and HIV/AIDS drugs may decrease oral contraceptive effectiveness.

Various studies give conflicting reports on the relationship between breast cancer and oral contraceptive use.

Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly if you started using hormonal contraceptives at a younger age.

After you stop using hormonal contraceptives, the chances of having breast cancer diagnosed begin to go down and disappear 10 years after stopping use of the pill. It is not known whether this slightly increased risk of having breast cancer diagnosed is caused by the pill. It may be that women taking the pill were examined more often, so that breast cancer was more likely to be detected.

You should have regular breast examinations by a healthcare provider and examine your own breasts monthly. Tell your healthcare provider if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is usually a hormone-sensitive tumor.

Some studies have found an increase in the incidence of cancer of the cervix in women who use oral

contraceptives. However, this finding may be related to factors other than the use of oral contraceptives.

Taking the pill provides some important noncontraceptive benefits. These include less painful menstruation, less menstrual blood loss and anemia, fewer pelvic infections, and fewer cancers of the ovary and the lining of the uterus.

Be sure to discuss any medical condition you may have with your healthcare provider. Your healthcare provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the healthcare provider believes that it is appropriate to postpone it. You should be reexamined at least once a year while taking oral contraceptives. The detailed patient information leaflet gives you further information which you should read and discuss with your healthcare provider.

## HOW TO TAKE THE PILL

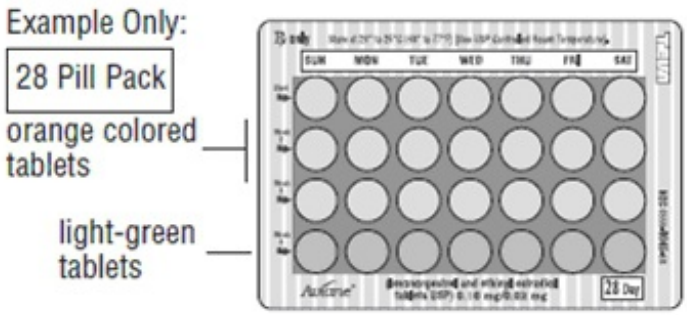
## IMPORTANT POINTS TO REMEMBER

*BEFORE* YOU START TAKING YOUR PILLS:

1. BE SURE TO READ THESE DIRECTIONS:
   Before you start taking your pills.
   And
   Anytime you are not sure what to do.
2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.
   If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant. See "**WHAT TO DO IF YOU MISS PILLS**" below.
3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1 TO 3 PACKS OF PILLS.
   If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your healthcare provider.
4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills.
   On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.
5. IF YOU HAVE VOMITING (within 4 hours after you take your pill), you should follow the instructions for **WHAT TO DO IF YOU MISS PILLS**. IF YOU HAVE DIARRHEA or IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well.
   Use a backup nonhormonal method (such as condoms or spermicide) until you check with your healthcare provider.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your healthcare provider about how to make pill-taking easier or about using another method of birth control.
7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your healthcare provider.

### *BEFORE* YOU START TAKING YOUR PILLS

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL. It is important to take it at about the same time every day.
2. LOOK AT YOUR PILL PACK:
   The *28 pill pack* has 21 "active" orange pills (with hormones) to take for 3 weeks, followed by 1 week of "reminder" light-green pills (without hormones).
3. FIND:
   1) where on the pack to start taking pills,
   2) in what order to take the pills (follow the arrows) and
   3) the week numbers printed on the pack.




4. BE SURE YOU HAVE READY AT ALL TIMES:
   ANOTHER KIND OF BIRTH CONTROL (such as condoms or spermicide) to use as a backup in case you miss pills.
   AN EXTRA, FULL PILL PACK.

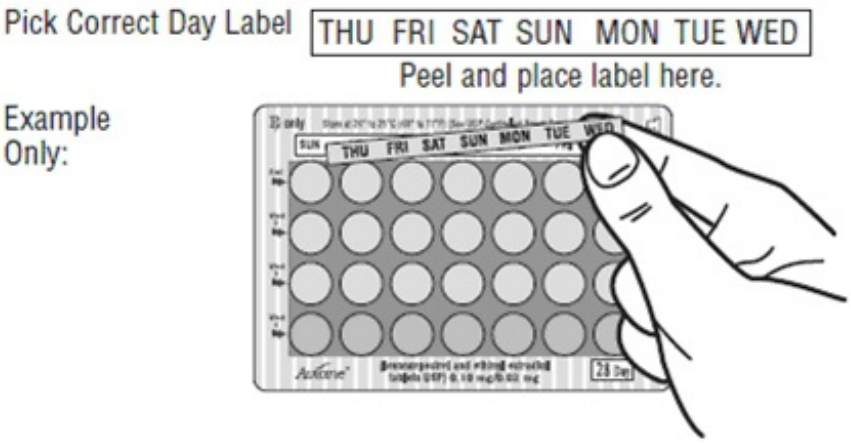
**WHEN TO START THE *FIRST* PACK OF PILLS**

You have a choice of which day to start taking your first pack of pills.

Decide with your healthcare provider which is the best day for you. Pick a time of day which will be easy to remember.

**DAY 1 START**

1. Pick the day label strip that starts with the first day of your period (this is the day you start bleeding or spotting, even if it is almost midnight when the bleeding begins).
2. Place this day label strip on the cycle tablet dispenser over the area that has the days of the week (starting with Sunday) printed on the dispensing card.




   Note: If the first day of your period is a Sunday, you can skip steps #1 and #2.
3. Take the first "active" orange pill of the first pack during the *first 24 hours of your period.*
4. You will not need to use a backup nonhormonal method of birth control, since you are starting the pill at the beginning of your period.

**SUNDAY START**

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

**WHAT TO DO DURING THE MONTH**

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

**IF YOU SWITCH FROM ANOTHER BRAND OF COMBINATION PILLS**

*If your previous brand had 21 pills:* Wait 7 days to start taking Aviane. You will probably have your period during that week. Be sure that no more than 7 days pass between the 21 day pack and taking the first orange Aviane pill ("active" with hormone).

*If your previous brand had 28 pills:* Start taking the first orange Aviane pill ("active" with hormone) on the day after your last "reminder" pill. Do not wait any days between packs.

**WHAT TO DO IF YOU MISS PILLS**

Aviane may not be as effective if you miss orange "active" pills, and particularly if you miss the first few or the last few orange "active" pills in a pack.

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

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.
2. You COULD BECOME PREGNANT if you have sex in the *7 days* after you restart your pills. You MUST use a nonhormonal birth control method (such as condoms or spermicide) as a backup for those 7 days.

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

1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You COULD BECOME PREGNANT if you have sex in the *7 days* after you restart your pills. You MUST use a nonhormonal birth control method (such as condoms or spermicide) as a backup for those 7 days.

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

1. ***If you are a Day 1 Starter:***
   THROW OUT the rest of the pill pack and start a new pack that same day.
   ***If you are a Sunday Starter:***
   Keep taking 1 pill every day until Sunday.
   On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected.
   However, if you miss your period 2 months in a row, call your healthcare provider because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex in the *7 days* after you restart your pills. You MUST use a nonhormonal birth control method (such as condoms or spermicide) as a backup for those 7 days.

If you **MISS 3 OR MORE** orange “active” pills in a row (during the first 3 weeks):

1. ***If you are a Day 1 Starter:***
   THROW OUT the rest of the pill pack and start a new pack that same day.
   ***If you are a Sunday Starter:***
   Keep taking 1 pill every day until Sunday.
   On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected.
   However, if you miss your period 2 months in a row, call your healthcare provider because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex in the *7 days* after you restart your pills.
   You MUST use a nonhormonal birth control method (such as condoms or spermicide) as a backup for those 7 days.

**If you forget any of the 7 light-green “reminder” pills in WEEK 4:**

THROW AWAY the pills you missed.

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

You do not need a backup nonhormonal birth control method if you start your next pack on time.

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

Use a BACKUP NONHORMONAL BIRTH CONTROL METHOD anytime you have sex.

KEEP TAKING ONE PILL EACH DAY until you can reach your healthcare provider.

**BIRTH CONTROL AFTER STOPPING THE PILL**

If you do not wish to become pregnant after stopping the pill, speak to your healthcare provider about another method of birth control.

**Teva Pharmaceuticals USA, Inc.**

North Wales, PA 19454

Rev. C 6/2020

**Aviane® 28 Tablets**
**(levonorgestrel and ethinyl estradiol tablets)**
**DETAILED PATIENT LABELING**

**This product (like all oral contraceptives) is intended to prevent pregnancy. Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases (STDs) such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.**

**INTRODUCTION**

Any woman who considers using oral contraceptives (the “birth control pill” or “the pill”) should understand the benefits and risks of using this form of birth control. This leaflet will give you much of the information you will need to make this decision and will also help you determine if you are at risk of developing any of the serious side effects of the pill. It will tell you how to use the pill properly so that it will be as effective as possible. However, this leaflet is not a replacement for a careful discussion between you and your healthcare provider. You should discuss the information provided in this leaflet with him or her, both when you first start taking the pill and during your revisits. You should also follow your healthcare provider's advice with regard to regular checkups while you are on the pill.

**EFFECTIVENESS OF ORAL CONTRACEPTIVES**

Oral contraceptives or “birth control pills” or “the pill” are used to prevent pregnancy and are more effective than most other nonsurgical methods of birth control. When they are taken correctly, without

missing any pills, the chance of becoming pregnant is approximately 1% per year (1 pregnancy per 100 women per year of use). Typical failure rates are approximately 5% per year (5 pregnancies per 100 women per year of use) when women who miss pills are included. The chance of becoming pregnant increases with each missed pill during each 28 day cycle of use.

In comparison, average failure rates for other methods of birth control during the first year of use are as follows:

| | |
|---|---|
| IUD: 0.1 to 2% | Female condom alone: 21% |
| Depo-Provera® (injectable progestogen): 0.3% | Cervical cap |
| Norplant® System (levonorgestrel implants): 0.05% | Never given birth: 20% |
| Diaphragm with spermicides: 20% | Given birth: 40% |
| Spermicides alone: 26% | Periodic abstinence: 25% |
| Male condom alone: 14% | No methods: 85% |

## WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES

**Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral contraceptive use. This risk increases with age and with the amount of smoking (15 or more cigarettes per day has been associated with a significantly increased risk) and is quite marked in women over 35 years of age. Women who use oral contraceptives should not smoke.**

Some women should not use the pill. For example, you should not take the pill if you have any of the following conditions:

- History of heart attack or stroke
- Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), or eyes
- A history of blood clots in the deep veins of your legs
- Chest pain (angina pectoris)
- Known or suspected breast cancer or cancer of the lining of the uterus, cervix or vagina, or certain hormonally-sensitive cancers
- Unexplained vaginal bleeding (until a diagnosis is reached by your healthcare provider)
- Liver tumor (benign or cancerous) or active liver disease
- Yellowing of the whites of the eyes or of the skin (jaundice) during pregnancy or during previous use of the pill
- Known or suspected pregnancy
- A need for surgery with prolonged bed rest
- Heart valve or heart rhythm disorders that may be associated with formation of blood clots
- Diabetes affecting your circulation
- Headaches with neurological symptoms
- Uncontrolled high blood pressure
- Allergy or hypersensitivity to any of the components of Aviane (levonorgestrel and ethinyl estradiol tablets)

Tell your healthcare provider if you have had any of these conditions. Your healthcare provider can recommend another method of birth control.

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

## OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

Tell your healthcare provider if you or any family member has ever had:

- Breast nodules, fibrocystic disease of the breast, an abnormal breast X-ray or mammogram
- Diabetes
- Elevated cholesterol or triglycerides
- High blood pressure
- A tendency to form blood clots
- Migraine or other headaches or epilepsy
- Depression
- Gallbladder, liver, heart, or kidney disease
- History of scanty or irregular menstrual periods

Women with any of these conditions should be checked often by their healthcare provider if they choose to use oral contraceptives. Also, be sure to inform your healthcare provider if you smoke or are on any medications.

Although cardiovascular disease risks may be increased with oral contraceptive use in healthy, nonsmoking women over 40 (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women.

## RISKS OF TAKING ORAL CONTRACEPTIVES

### 1. Risks of Developing Blood Clots

Blood clots and blockage of blood vessels are the most serious side effects of taking oral contraceptives and can cause death or serious disability. In particular, a clot in the legs can cause thrombophlebitis and a clot that travels to the lungs can cause a sudden blocking of the vessel carrying blood to the lungs. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.

Users of combination oral contraceptives have a higher risk of developing blood clots compared to nonusers. This risk is highest during the first year of combination oral contraceptive use.

If you take oral contraceptives and need elective surgery, need to stay in bed for a prolonged illness or injury, or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your healthcare provider about stopping oral contraceptives three to four weeks before surgery and not taking oral contraceptives for two weeks after surgery or during bed rest. You should also not take oral contraceptives soon after delivery of a baby or after a midtrimester pregnancy termination. It is advisable to wait for at least four weeks after delivery if you are not breastfeeding. If you are breastfeeding, you should wait until you have weaned your child before using the pill (see also the section **While Breastfeeding** in **GENERAL PRECAUTIONS**).

The risk of blood clots is greater in users of combination oral contraceptives compared to nonusers. This risk may be higher in users of high-dose pills (those containing 50 mcg or more of estrogen) and may also be greater with longer use. In addition, some of these increased risks may continue for a number of years after stopping combination oral contraceptives. The risk of abnormal blood clotting increases with age in both users and nonusers of combination oral contraceptives, but the increased risk from the oral contraceptive appears to be present at all ages.

The excess risk of blood clots is highest during the first year a woman ever uses a combined oral contraceptive. This increased risk is lower than blood clots associated with pregnancy. The use of combination oral contraceptives also increases the risk of other clotting disorders, including heart attack and stroke. Blood clots in veins cause death in 1% to 2% of cases. The risk of clotting is further increased in women with other conditions. Examples include: smoking, high blood pressure, abnormal lipid levels, certain inherited or acquired clotting disorders, obesity, surgery or injury, recent delivery or second trimester abortion, prolonged inactivity or bed rest. If possible, combination oral contraceptives should be stopped before surgery and during prolonged inactivity or bed rest.

Cigarette smoking increases the risk of serious cardiovascular events. This risk increases with age and

amount of smoking and is quite pronounced in women over 35. Women who use combination oral contraceptives should be strongly advised not to smoke. If you smoke you should talk to your healthcare professional before taking combination oral contraceptives.

**2. Heart Attacks and Strokes**

Oral contraceptives may increase the tendency to develop strokes or transient ischemic attacks (blockage or rupture of blood vessels in the brain) and angina pectoris and heart attacks (blockage of blood vessels in the heart). Any of these conditions can cause death or serious disability.

Smoking greatly increases the possibility of suffering heart attacks and strokes. Furthermore, smoking and the use of oral contraceptives greatly increase the chances of developing and dying of heart disease.

Women with migraine (especially migraine/headache with neurological symptoms) who take oral contraceptives also may be at higher risk of stroke and must not use combination oral contraceptives (see section **WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES**).

**3. Gallbladder Disease**

Oral contraceptive users probably have a greater risk than nonusers of having gallbladder disease, although this risk may be related to pills containing high doses of estrogens. Oral contraceptives may worsen existing gallbladder disease or accelerate the development of gallbladder disease in women previously without symptoms.

**4. Liver Tumors**

In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, a possible but not definite association has been found with the pill and liver cancers in two studies in which a few women who developed these very rare cancers were found to have used oral contraceptives for long periods. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.

**5. Cancer of the Reproductive Organs and Breasts**

Various studies give conflicting reports on the relationship between breast cancer and oral contraceptive use.

Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly if you started using hormonal contraceptives at a younger age.

After you stop using hormonal contraceptives, the chances of having breast cancer diagnosed begin to go down and disappear 10 years after stopping use of the pill. It is not known whether this slightly increased risk of having breast cancer diagnosed is caused by the pill. It may be that women taking the pill were examined more often, so that breast cancer was more likely to be detected.

You should have regular breast examinations by a healthcare provider and examine your own breasts monthly. Tell your healthcare provider if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is usually a hormone-sensitive tumor.

Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives.

**6. Lipid Metabolism and Pancreatitis**

There have been reports of increases of blood cholesterol and triglycerides in users of combination oral contraceptives. Increases in triglycerides have led to inflammation of the pancreas (pancreatitis) in some cases.

## ESTIMATED RISK OF DEATH FROM A BIRTH CONTROL METHOD OR PREGNANCY

All methods of birth control and pregnancy are associated with a risk of developing certain diseases which may lead to disability or death. An estimate of the number of deaths associated with different methods of birth control and pregnancy has been calculated and is shown in the following table.

**ANNUAL NUMBER OF BIRTH RELATED OR METHOD RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NONSTERILE WOMEN, BY FERTILITY CONTROL METHOD AND ACCORDING TO AGE**

| Method of control and outcome | 15 to 19 | 20 to 24 | 25 to 29 | 30 to 34 | 35 to 39 | 40 to 44 |
|---|---|---|---|---|---|---|
| No fertility control methods * | 7.0 | 7.4 | 9.1 | 14.8 | 25.7 | 28.2 |
| Oral contraceptives nonsmoker ** | 0.3 | 0.5 | 0.9 | 1.9 | 13.8 | 31.6 |
| Oral contraceptives smoker ** | 2.2 | 3.4 | 6.6 | 13.5 | 51.1 | 117.2 |
| IUD ** | 0.8 | 0.8 | 1.0 | 1.0 | 1.4 | 1.4 |
| Condom * | 1.1 | 1.6 | 0.7 | 0.2 | 0.3 | 0.4 |
| Diaphragm/spermicide * | 1.9 | 1.2 | 1.2 | 1.3 | 2.2 | 2.8 |
| Periodic abstinence * | 2.5 | 1.6 | 1.6 | 1.7 | 2.9 | 3.6 |

* Deaths are birth related

** Deaths are method related

In the above table, the risk of death from any birth control method is less than the risk of childbirth, except for oral contraceptive users over the age of 35 who smoke and pill users over the age of 40 even if they do not smoke. It can be seen in the table that for women aged 15 to 39, the risk of death was highest with pregnancy (7 to 26 deaths per 100,000 women, depending on age). Among pill users who do not smoke, the risk of death was always lower than that associated with pregnancy for any age group, except for those women over the age of 40, when the risk increases to 32 deaths per 100,000 women, compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35, the estimated number of deaths exceeds those for other methods of birth control. If a woman is over the age of 40 and smokes, her estimated risk of death is four times higher (117/100,000 women) than the estimated risk associated with pregnancy (28/100,000 women) in that age group.

The suggestion that women over 40 who do not smoke should not take oral contraceptives is based on information from older high-dose pills. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of oral contraceptive use by healthy, nonsmoking women over 40 years of age may outweigh the possible risks. Older women, as all women, who take oral contraceptives, should take an oral contraceptive which contains the least amount of estrogen and progestogen that is compatible with the individual patient needs.

## WARNING SIGNALS

If any of these adverse effects occur while you are taking oral contraceptives, call your healthcare provider immediately:

- Sharp chest pain, coughing of blood, or sudden shortness of breath (indicating a possible clot in the lung)
- Pain in the calf (indicating a possible clot in the leg)
- Crushing chest pain or heaviness in the chest (indicating a possible heart attack)
- Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness, or numbness in an arm or leg (indicating a possible stroke)
- Sudden partial or complete loss of vision (indicating a possible clot in the eye)
- Breast lumps (indicating possible breast cancer or fibrocystic disease of the breast; ask your

healthcare provider to show you how to examine your breasts)
- Severe pain or tenderness in the stomach area (indicating a possibly ruptured liver tumor)
- Difficulty in sleeping, weakness, lack of energy, fatigue, or change in mood (possibly indicating severe depression)
- Jaundice or a yellowing of the skin or eyeballs, accompanied frequently by fever, fatigue, loss of appetite, dark-colored urine, or light-colored bowel movements (indicating possible liver problems)

## SIDE EFFECTS OF ORAL CONTRACEPTIVES

### 1. Unscheduled or Breakthrough Vaginal Bleeding or Spotting

Unscheduled vaginal bleeding or spotting may occur while you are taking the pills. Unscheduled bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Unscheduled bleeding occurs most often during the first few months of oral contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue taking your pills on schedule. If the bleeding occurs in more than one cycle or lasts for more than a few days, talk to your healthcare provider.

### 2. Contact Lenses

If you wear contact lenses and notice a change in vision or an inability to wear your lenses, contact your healthcare provider.

### 3. Fluid Retention

Oral contraceptives may cause edema (fluid retention) with swelling of the fingers or ankles and may raise your blood pressure. If you experience fluid retention, contact your healthcare provider.

### 4. Melasma

A spotty darkening of the skin is possible, particularly of the face.

### 5. Other Side Effects

Other side effects may include nausea, breast tenderness, change in appetite, headache, nervousness, depression, dizziness, loss of scalp hair, rash, vaginal infections, inflammation of the pancreas, and allergic reactions.

If any of these side effects bother you, call your healthcare provider.

## GENERAL PRECAUTIONS

### 1. Missed Periods and Use of Oral Contraceptives Before or During Early Pregnancy

There may be times when you may not menstruate regularly after you have completed taking a cycle of pills. If you have taken your pills regularly and miss one menstrual period, continue taking your pills for the next cycle but be sure to inform your healthcare provider before doing so. If you have not taken the pills daily as instructed and missed a menstrual period, or if you missed two consecutive menstrual periods, you may be pregnant. Check with your healthcare provider immediately to determine whether you are pregnant. Stop taking oral contraceptives if you are pregnant.

There is no conclusive evidence that oral contraceptive use is associated with an increase in birth defects, when taken inadvertently during early pregnancy. Previously, a few studies had reported that oral contraceptives might be associated with birth defects, but these studies have not been confirmed. Nevertheless, oral contraceptives should not be used during pregnancy. You should check with your healthcare provider about risks to your unborn child of any medication taken during pregnancy.

### 2. While Breastfeeding

If you are breastfeeding, consult your healthcare provider before starting oral contraceptives. Some of the drug will be passed on to the child in the milk. A few adverse effects on the child have been

reported, including yellowing of the skin (jaundice) and breast enlargement. In addition, oral contraceptives may decrease the amount and quality of your milk. If possible, do not use oral contraceptives while breastfeeding. You should use another method of contraception since breastfeeding provides only partial protection from becoming pregnant and this partial protection decreases significantly as you breastfeed for longer periods of time. You should consider starting oral contraceptives only after you have weaned your child completely.

**3. Laboratory Tests**

If you are scheduled for any laboratory tests, tell your doctor you are taking birth control pills. Certain blood tests may be affected by birth control pills.

**4. Drug Interactions**

Certain drugs may interact with birth control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Such drugs include rifampin, drugs used for epilepsy such as barbiturates (for example, phenobarbital) and phenytoin (Dilantin® is one brand of this drug), primidone (Mysoline®), topiramate (Topamax®), carbamazepine (Tegretol® is one brand of this drug), phenylbutazone (Butazolidin® is one brand), some drugs used for HIV or AIDS such as ritonavir (Norvir®), modafinil (Provigil®) and possibly certain antibiotics (such as ampicillin and other penicillins, and tetracyclines), and herbal products containing St. John's Wort (Hypericum perforatum). You may also need to use a nonhormonal method of contraception during any cycle in which you take drugs that can make oral contraceptives less effective.

You may be at higher risk of a specific type of liver dysfunction if you take troleandomycin and oral contraceptives at the same time.

You should inform your healthcare provider about all medicines you are taking, including nonprescription products.

**5. Sexually Transmitted Diseases**

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

**HOW TO TAKE THE PILL**

**IMPORTANT POINTS TO REMEMBER**

*BEFORE* YOU START TAKING YOUR PILLS:

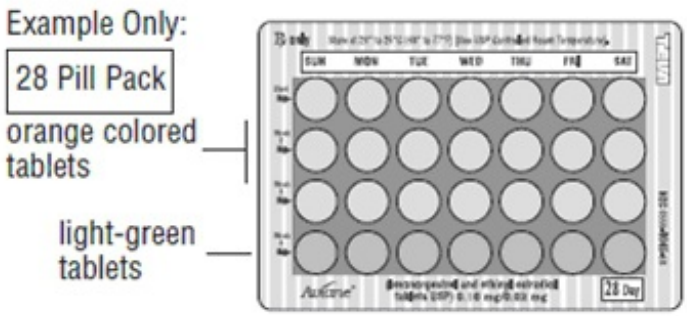
1. BE SURE TO READ THESE DIRECTIONS:
   Before you start taking your pills.
   And
   Anytime you are not sure what to do.
2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.
   If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant. See "**WHAT TO DO IF YOU MISS PILLS**" below.
3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1 TO 3 PACKS OF PILLS.
   If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your healthcare provider.
4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills.
   On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.
5. IF YOU HAVE VOMITING (within 4 hours after you take your pill), you should follow the instructions for **WHAT TO DO IF YOU MISS PILLS**. IF YOU HAVE DIARRHEA or IF YOU

TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well.
Use a backup nonhormonal method (such as condoms or spermicide) until you check with your healthcare provider.

6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your healthcare provider about how to make pill-taking easier or about using another method of birth control.
7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, contact your healthcare provider.

**_BEFORE_ YOU START TAKING YOUR PILLS**

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL. It is important to take it at about the same time every day.
2. LOOK AT YOUR PILL PACK:
   The *28 pill pack* has 21 “active” orange pills (with hormones) to take for 3 weeks, followed by 1 week of "reminder" light-green pills (without hormones).
3. FIND:
   1) where on the pack to start taking pills,
   2) in what order to take the pills (follow the arrows) and
   3) the week numbers printed on the pack.




4. BE SURE YOU HAVE READY AT ALL TIMES:
   ANOTHER KIND OF BIRTH CONTROL (such as condoms or spermicide) to use as a backup in case you miss pills.
   AN EXTRA, FULL PILL PACK.

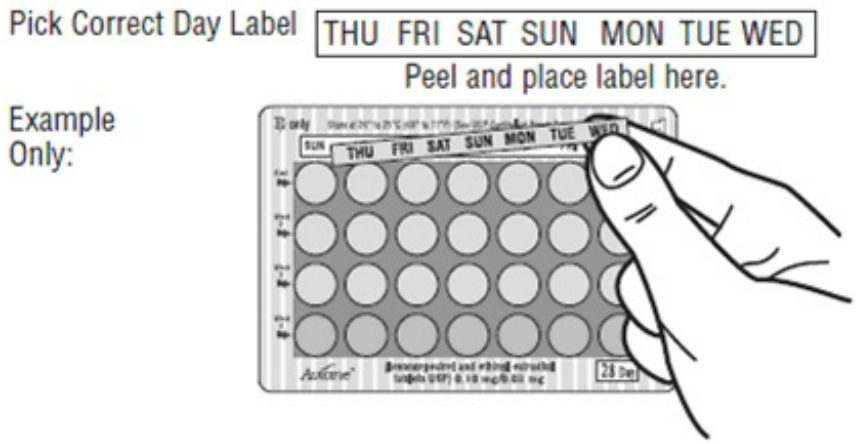
**WHEN TO START THE _FIRST_ PACK OF PILLS**

You have a choice of which day to start taking your first pack of pills.

Decide with your healthcare provider which is the best day for you. Pick a time of day which will be easy to remember.

**DAY 1 START:**

1. Pick the day label strip that starts with the first day of your period (this is the day you start bleeding or spotting, even if it is almost midnight when the bleeding begins).
2. Place this day label strip on the cycle tablet dispenser over the area that has the days of the week (starting with Sunday) printed on the dispensing card.




Note: If the first day of your period is a Sunday, you can skip steps #1 and #2.

3. Take the first "active" orange pill of the first pack during the *first 24 hours of your period.*
4. You will not need to use a backup nonhormonal method of birth control, since you are starting the pill at the beginning of your period.

**SUNDAY START:**

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

**WHAT TO DO DURING THE MONTH**

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

**IF YOU SWITCH FROM ANOTHER BRAND OF COMBINATION PILLS:**

*If your previous brand had 21 pills:* Wait 7 days to start taking Aviane. You will probably have your period during that week. Be sure that no more than 7 days pass between the 21 day pack and taking the first orange Aviane pill ("active" with hormone).

*If your previous brand had 28 pills:* Start taking the first orange Aviane pill ("active" with hormone) on the day after your last "reminder" pill. Do not wait any days between packs.

**WHAT TO DO IF YOU MISS PILLS**

Aviane may not be as effective if you miss orange "active" pills, and particularly if you miss the first few or the last few orange "active" pills in a pack.

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

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.
2. You COULD BECOME PREGNANT if you have sex in the *7 days* after you restart your pills. You MUST use a nonhormonal birth control method (such as condoms or spermicide) as a backup for those 7 days.

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

1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You COULD BECOME PREGNANT if you have sex in the *7 days* after you restart your pills. You MUST use a nonhormonal birth control method (such as condoms or spermicide) as a backup for those 7 days.

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

1. ***If you are a Day 1 Starter:***
   THROW OUT the rest of the pill pack and start a new pack that same day.
   ***If you are a Sunday Starter:***
   Keep taking 1 pill every day until Sunday.
   On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected.
   However, if you miss your period 2 months in a row, call your healthcare provider because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex in the *7 days* after you restart your pills. You MUST use a nonhormonal birth control method (such as condoms or spermicide) as a backup for those 7 days.

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

1. ***If you are a Day 1 Starter:***
   THROW OUT the rest of the pill pack and start a new pack that same day.
   ***If you are a Sunday Starter:***
   Keep taking 1 pill every day until Sunday.
   On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected.
   However, if you miss your period 2 months in a row, call your healthcare provider because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex in the *7 days* after you restart your pills. You MUST use a nonhormonal birth control method (such as condoms or spermicide) as a backup for those 7 days.

**If you forget any of the 7 light-green "reminder" pills in WEEK 4:**

THROW AWAY the pills you missed.

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

You do not need a backup nonhormonal birth control method if you start your next pack on time.

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

Use a BACKUP NONHORMONAL BIRTH CONTROL METHOD anytime you have sex.

KEEP TAKING ONE PILL EACH DAY until you can reach your healthcare provider.

**PREGNANCY DUE TO PILL FAILURE**

The incidence of pill failure resulting in pregnancy is approximately 1 per year (1 pregnancy per 100 women per year of use) if taken every day as directed, but the more typical failure rate is approximately 5% per year (5 pregnancies per 100 women per year of use) including women who do not always take the pill exactly as directed without missing any pills. If you do become pregnant, the risk to the fetus is minimal, but you should stop taking your pills and discuss the pregnancy with your healthcare provider.

**PREGNANCY AFTER STOPPING THE PILL**

There may be some delay in becoming pregnant after you stop using oral contraceptives, especially if you had irregular menstrual cycles before you used oral contraceptives. It may be advisable to postpone conception until you begin menstruating regularly once you have stopped taking the pill and desire pregnancy.

There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.

**BIRTH CONTROL AFTER STOPPING THE PILL**

If you do not wish to become pregnant after stopping the pill, you should use another method of birth control immediately after stopping Aviane. Speak to your healthcare provider about another method of birth control.

**OVERDOSAGE**

Overdosage may cause nausea, vomiting, breast tenderness, dizziness, abdominal pain and fatigue/drowsiness. Withdrawal bleeding may occur in females. In case of overdosage, contact your healthcare provider or pharmacist.

**OTHER INFORMATION**

Your healthcare provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and your healthcare provider believes that it is appropriate to postpone it. You should be reexamined at least once a year. Be sure to inform your healthcare provider if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your healthcare provider, because this is a time to determine if there are early signs of side effects of oral contraceptive use.

Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth control pills.

**HEALTH BENEFITS FROM ORAL CONTRACEPTIVES**

In addition to preventing pregnancy, use of oral contraceptives may provide certain benefits. They are:

- Menstrual cycles may become more regular
- Blood flow during menstruation may be lighter, and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur.
- Pain or other symptoms during menstruation may be encountered less frequently
- Ovarian cysts may occur less frequently
- Ectopic (tubal) pregnancy may occur less frequently
- Noncancerous cysts or lumps in the breast may occur less frequently
- Acute pelvic inflammatory disease may occur less frequently
- Oral contraceptive use may provide some protection against developing two forms of cancer: cancer of the ovaries and cancer of the lining of the uterus.

If you want more information about birth control pills, ask your healthcare provider or pharmacist. They have a more technical leaflet called the Professional Labeling which you may wish to read.

**Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

All brand names listed are the registered trademarks of their respective owners and are not trademarks of Teva Pharmaceuticals USA.

**Teva Pharmaceuticals USA, Inc.**

North Wales, PA 19454

Rev. C 6/2020

**Package/Label Display Panel, Part 1 of 2**

30100940

Non Varnish Area
For Lot/Exp

NDC 0555-**9045**-58

**6** Blister Cards, 28 Tablets Each

Aviane®

(levonorgestrel and ethinyl estradiol tablets USP)
**0.10 mg/0.02 mg**

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

NDC 0555-**9045**-58

**6** Blister Cards, 28 Tablets Each

Aviane®

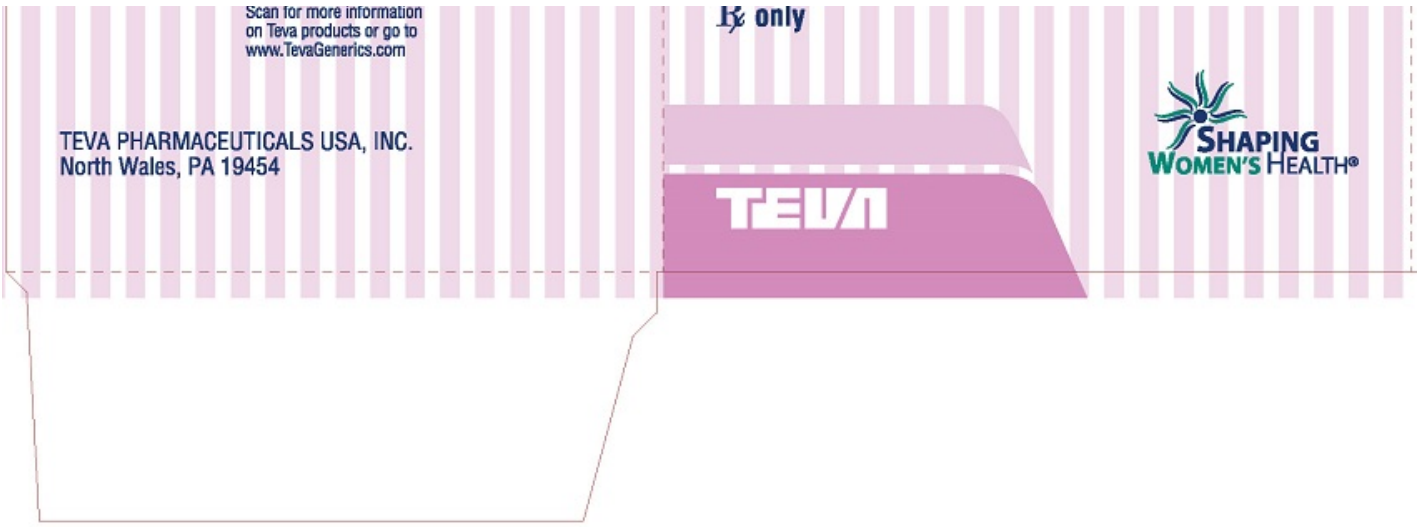
(levonorgestrel and ethinyl estradiol tablets USP)
**0.10 mg/0.02 mg**

**Usual Dosage:** One orange tablet daily for 21 consecutive days followed by one light-green inert tablet for seven consecutive days, according to prescribed schedule.

See enclosed package insert for full prescribing information.

**After removing the aluminum-foil overwrap, avoid humid conditions and protect from light by storing the dispenser card in the opaque vinyl folder provided.**

**To the Dispenser:** This carton contains one combination labeling piece of information intended for the patient. Informational pieces are to be provided to the patient with each prescription.




**Package/Label Display Panel, Part 2 of 2**

NDC 0555-**9045**-58

**6** Blister Cards, 28 Tablets Each

# Aviane®

## (levonorgestrel and ethinyl estradiol tablets USP)

## 0.10 mg/0.02 mg

**THIS PRODUCT (LIKE ALL ORAL CONTRACEPTIVES) IS INTENDED TO PREVENT PREGNANCY. IT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.**

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3 0555-9045-58 9

799-30-100940

Rev. A 2/2016

NDC 0555-**9045**-58

**6** Blister Cards, 28 Tablets Each

Aviane®

(levonorgestrel and ethinyl estradiol tablets USP)

0.10 mg/0.02 mg

Contains 6 blister cards, each containing 28 tablets. Twenty-one orange tablets, each containing 0.10 mg levonorgestrel, USP with 0.02 mg ethinyl estradiol, USP and seven light-green inert tablets.

℞ only

TEVA

SHAPING WOMEN'S HEALTH®

NO PRINT/
NO VARNISH AREA

Non Varnish Area
For Lot/Exp

**Aviane® (levonorgestrel and ethinyl estradiol tablets USP) 6 Blister Cards; 28 Tablets Each, Carton Text**

**NDC** 0555-**9045**-58

**6 Blister Cards, 28 Tablets Each**

***Aviane®***

**(levonorgestrel and ethinyl**

**estradiol tablets USP)**

**0.10 mg/0.02 mg**

Contains 6 blister cards, each containing 28 tablets. Twenty-one orange tablets, each containing 0.10 mg levonorgestrel, USP with 0.02 mg ethinyl estradiol, USP and seven light-green inert tablets.

**Rx only**

**SHAPING**

**WOMEN'S HEALTH®**

**TEVA**

# AVIANE

levonorgestrel and ethinyl estradiol kit

| Product Information | | | |
|---|---|---|---|
| **Product Type** | HUMAN PRESCRIPTION DRUG | **Item Code (Source)** | NDC:0555-9045 |

| Packaging | | | | |
|---|---|---|---|---|
| **#** | **Item Code** | **Package Description** | **Marketing Start Date** | **Marketing End Date** |
| **1** | NDC:0555-9045-58 | 6 in 1 CARTON | 04/02/2001 | |
| **1** | NDC:0555-9045-79 | 1 in 1 POUCH | | |
| **1** | | 1 in 1 BLISTER PACK; Type 0: Not a Combination Product | | |

| Quantity of Parts | | |
|---|---|---|
| **Part #** | **Package Quantity** | **Total Product Quantity** |
| **Part 1** | | 21 |
| **Part 2** | | 7 |

## Part 1 of 2

# LEVONORGESTREL AND ETHINYL ESTRADIOL

levonorgestrel and ethinyl estradiol tablet, film coated

### Product Information

| | |
|---|---|
| **Route of Administration** | ORAL |

### Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|---|---|---|
| **LEVONORGESTREL** (UNII: 5W7SIA7YZW) (LEVONORGESTREL - UNII:5W7SIA7YZW) | LEVONORGESTREL | 0.1 mg |
| **ETHINYL ESTRADIOL** (UNII: 423D2T571U) (ETHINYL ESTRADIOL - UNII:423D2T571U) | ETHINYL ESTRADIOL | 0.02 mg |

### Inactive Ingredients

| Ingredient Name | Strength |
|---|---|
| **FD&C YELLOW NO. 6** (UNII: H77VEI93A8) | |
| **HYPROMELLOSE 2910 (15 MPA.S)** (UNII: 36SFW2JZ0W) | |
| **LACTOSE MONOHYDRATE** (UNII: EWQ57Q8I5X) | |
| **MAGNESIUM STEARATE** (UNII: 70097M6I30) | |
| **MICROCRYSTALLINE CELLULOSE** (UNII: OP1R32D61U) | |
| **POLYETHYLENE GLYCOL 4000** (UNII: 4R4HFI6D95) | |
| **STARCH, CORN** (UNII: O8232NY3SJ) | |
| **SODIUM STARCH GLYCOLATE TYPE A POTATO** (UNII: 5856J3G2A2) | |
| **TITANIUM DIOXIDE** (UNII: 15FIX9V2JP) | |

### Product Characteristics

| | | | |
|---|---|---|---|
| **Color** | ORANGE | **Score** | no score |
| **Shape** | ROUND | **Size** | 6mm |
| **Flavor** | | **Imprint Code** | dp;016 |
| **Contains** | | | |

## Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|---|---|---|---|
| ANDA | ANDA075796 | 04/02/2001 | |

## Part 2 of 2

## INERT

inert tablet

### Product Information

| | |
|---|---|
| **Route of Administration** | ORAL |

### Inactive Ingredients

| Ingredient Name | Strength |
|---|---|
| **D&C YELLOW NO. 10** (UNII: 35SW5USQ3G) | |
| **FD&C BLUE NO. 1** (UNII: H3R47K3TBD) | |
| **FD&C YELLOW NO. 6** (UNII: H77VEI93A8) | |

| | |
|---|---|
| **LACTOSE MONOHYDRATE** (UNII: EWQ57Q8I5X) | |
| **MAGNESIUM STEARATE** (UNII: 70097M6I30) | |
| **MICROCRYSTALLINE CELLULOSE** (UNII: OP1R32D61U) | |
| **STARCH, CORN** (UNII: O8232NY3SJ) | |

## Product Characteristics

| | | | |
|---|---|---|---|
| **Color** | GREEN (light-green) | **Score** | no score |
| **Shape** | ROUND | **Size** | 6mm |
| **Flavor** | | **Imprint Code** | dp;519 |
| **Contains** | | | |

## Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|---|---|---|---|
| ANDA | ANDA075796 | 04/02/2001 | |


## Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|---|---|---|---|
| ANDA | ANDA075796 | 04/02/2001 | |

**Labeler -** Teva Pharmaceuticals USA, Inc. (001627975)

Revised: 7/2020 Teva Pharmaceuticals USA, Inc.