ARANELLE- norethindrone and ethinyl estradiol
Teva Pharmaceuticals USA, Inc.

Aranelle® (norethindrone and ethinyl estradiol tablets USP)

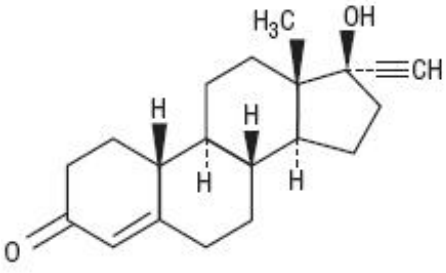
Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DESCRIPTION

Aranelle® 28-Day Regimen (norethindrone and ethinyl estradiol tablets USP) provides a continuous oral contraceptive regimen of 7 light yellow tablets, 9 white tablets, 5 more light yellow tablets, and then 7 peach tablets. Each light yellow tablet contains norethindrone, USP 0.5 mg and ethinyl estradiol, USP 0.035 mg, each white tablet contains norethindrone, USP 1 mg and ethinyl estradiol, USP 0.035 mg, and each peach tablet contains inert ingredients.

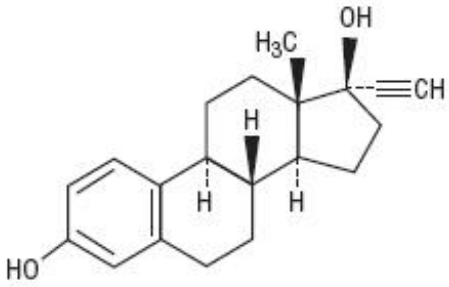
Norethindrone, USP is a potent progestational agent with the chemical name 17-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one. Ethinyl estradiol, USP is an estrogen with the chemical name 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol. Their structural formulae follow.

Norethindrone, USP



$C_{20}H_{26}O_2$ Molecular Weight: 298.42

Ethinyl Estradiol, USP



$C_{20}H_{24}O_2$ Molecular Weight: 296.40

The light yellow tablet contains the following inactive ingredients, D&C yellow no. 10 aluminum lake, lactose monohydrate, magnesium stearate, and pregelatinized starch.

The white tablet contains the following inactive ingredients, lactose monohydrate, magnesium stearate, and pregelatinized starch.

The inactive peach tablets contain the following inactive ingredients, anhydrous lactose, FD&C yellow no. 6 aluminum lake, magnesium stearate, microcrystalline cellulose, and pregelatinized starch.

CLINICAL PHARMACOLOGY

Combination oral contraceptives act by suppression of gonadotrophins. 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 may reduce the likelihood of implantation).

INDICATIONS AND USAGE

Oral contraceptives are indicated for the prevention of pregnancy in women who elect to use this product as a method of contraception.

Oral contraceptive products which contain 50 mcg of estrogen, should not be used unless medically indicated.

Oral contraceptives are highly effective. Table I lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception.[1] The efficacy of these contraceptive methods, except sterilization, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

TABLE I

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 First Year of Use		% of Women Continuing Use at One Year[C]
Method (1)	**Typical Use[A] (2)**	**Perfect Use[B] (3)**	**(4)**
Chance[D]	85	85	
Spermicides[E]	26	6	40
Periodic abstinence	25		63
Calendar		9	
Ovulation method		3	
Sympto-thermal[F]		2	
Post-ovulation		1	
Withdrawal	19	4	
Cap[G]			
Parous women	40	26	42
Nulliparous women	20	9	56
Sponge			
Parous women	40	20	42
Nulliparous women	20	9	56
Diaphragm[G]	20	6	56
Condom[H]			
Female (Reality)	21	5	56
Male	14	3	61

Pill	5		71
Progestin only		0.5	
Combined		0.1	
IUD			
Progesterone T	2	1.5	81
Copper T 380A	0.8	0.6	78
LNg 20	0.1	0.1	81
Depo-Provera	0.3	0.3	70
Norplant and Norplant-2	0.05	0.05	88
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.10	100

Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.[I]

Lactational Amenorrhea Method: LAM is a highly effective, *temporary* method of contraception.[J]

Source: Trussell J, Contraceptive Efficacy Table from Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Kowal D, Guest F, *Contraceptive Technology: Seventeenth Revised Edition.* New York, NY: Irvington Publishers, 1998.
(A) 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.
(B) 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.
(C) Among couples attempting to avoid pregnancy, the percentage who continue to use a method for one year.
(D) 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.

(E) Foams, creams, gels, vaginal suppositories, and vaginal film.
(F) Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.
(G) With spermicidal cream or jelly.
(H) Without spermicides.
(I) The treatment schedule is one dose within 72 hours after unprotected intercourse and a second dose 12 hours after the first dose. The Food and Drug Administration has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral (1 dose is 2 white pills), Alesse (1 dose is 5 pink pills), Nordette or Levlen (1 dose is 2 light-orange pills), Lo/Ovral (1 dose is 4 white pills), Triphasil or Tri-Levlen (1 dose is 4 yellow pills).
(J) 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 six months of age.

CONTRAINDICATIONS

Aranelle is contraindicated in females who are known to have or develop the following conditions:

- Thrombophlebitis or thromboembolic disorders
- A past history of deep vein thrombophlebitis or thromboembolic disorders
- Cerebral vascular or coronary artery disease
- Current diagnosis of, or history of, breast cancer, which may be hormone-sensitive
- 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, carcinomas or benign liver tumors
- Known or suspected pregnancy
- Are receiving Hepatitis C 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).**

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) 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 myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, 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 hypertension, hyperlipidemias, hypercholesterolemia, obesity and diabetes.[2-5]

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 formulations of both estrogens and progestogens than those in common use today.[6-11] The effect of long-term use of the oral contraceptives with lower formulations 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 a disease. Relative risk, the *ratio* of the incidence of a disease among oral contraceptive users to that among non-users, cannot be assessed directly from case control studies, but the odds ratio obtained is a measure of relative risk. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide not only a measure of the relative risk but a measure of attributable risk, which is the *difference* in the incidence of disease between oral contraceptive users and non-users. The attributable risk does provide information about the actual occurrence of a disease in the population (adapted from ref. 12 and 13 with the author's permission). For further information, the reader is referred to a text on epidemiological methods.

1. Thromboembolic Disorders and Other Vascular Problems

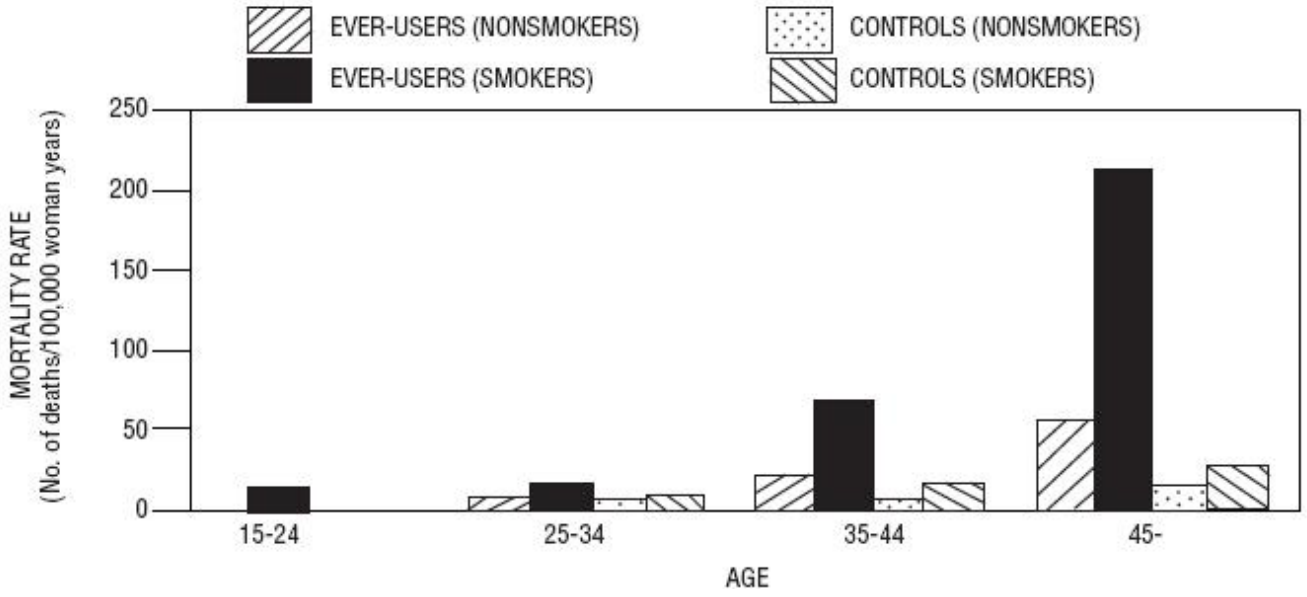
a. Myocardial Infarction

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.[2-5, 13] The relative risk of heart attack for current oral contraceptive users has been estimated to be 2 to 6.[2, 14-19] The risk is very low under the age of 30. However, there is the possibility of a risk of cardiovascular disease even in very young women who take oral contraceptives.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older, with smoking accounting for the majority of excess cases.[20]

Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and non-smokers over the age of 40 among women who use oral contraceptives (see Table II).[16]

TABLE 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, Table V[16]

Oral contraceptives may compound the effects of well-known risk factors such as hypertension, diabetes, hyperlipidemias, hypercholesterolemia, age and obesity.[3, 13, 21] In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism.[21-25] Oral contraceptives have been shown to increase blood pressure among users (see **WARNINGS, Elevated Blood Pressure**). 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. Thromboembolism

An increased risk of 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 non-users 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.[12, 13, 26-31] 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.[32] The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped.[12]

A 2- to 6-fold increase in relative risk of post-operative 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.[83] If feasible, oral contraceptives should be discontinued at least 4 weeks prior to and for 2 weeks after elective surgery and during and following prolonged immobilization. Since the immediate postpartum period also is associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than 4 to 6 weeks after delivery in women who elect not to breast feed.[33]

c. Cerebrovascular Diseases

An increase in both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes) has been shown in users of oral contraceptives. 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 non-users for both types of strokes while smoking interacted to increase the risk for hemorrhagic strokes.[34]

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.[35] The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers 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.[35] The attributable risk also is greater in women in their mid-thirties or older and among smokers.[13]

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.[36-38] A decline in serum high density lipoproteins (HDL) has been reported with many progestational agents.[22-24] A decline in serum high density lipoproteins has been associated with an increased incidence of ischemic heart disease.[39] 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 progestogens used in the contraceptives. The amount of both hormones should be considered in the choice of an oral contraceptive.[37]

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 that produces satisfactory results for the individual. Products containing 50 mcg estrogen should be used only when medically indicated.

e. Persistence of Risk of Vascular Disease

There are three studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives.[17, 34, 40] 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 5 or more years, but this increased risk was not demonstrated in other age groups.[17] 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.[40] There is a significantly increased relative risk of subarachnoid hemorrhage after termination of use of oral contraceptives.[34] However, these studies were performed with oral contraceptive formulations containing 50 mcg or higher of estrogen. Products containing 50 mcg estrogen should be used only when medically indicated.

2. Estimates of Mortality from Contraceptive Use

One study gathered data from a variety of sources which have estimated the mortality rates associated with different methods of contraception at different ages (see Table III).[41] 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 low and below 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 1970s -- but not reported in the U.S. until 1983.[16, 41] 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,[78, 79] 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 non-smoking 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 non-smoking 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.[80]

TABLE III

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

			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*(A)*	7	7.4	9.1	14.8	25.7	28.2
Oral contraceptives						
non-smoker*(B)*	0.3	0.5	0.9	1.9	13.8	31.6
smoker*(B)*	2.2	3.4	6.6	13.5	51.1	117.2
IUD*(B)*	0.8	0.8	1	1	1.4	1.4
Condom*(A)*	1.1	1.6	0.7	0.2	0.3	0.4

Diaphragm/Spermicide[(A)]	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence[(A)]	2.5	1.6	1.6	1.7	2.9	3.6

(A) Deaths are birth-related

(B) Deaths are method-related

Estimates adapted from H.W. Ory, Table 3[41]

3. Malignant Neoplasms

Breast Cancer

Aranelle is contraindicated in females who currently have or have had breast cancer because breast cancer may be hormonally sensitive (see **CONTRAINDICATIONS**).

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

Cervical Cancer

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women.[50-53] 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 oral contraceptive use and breast or 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 benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases per 100,000 for users, a risk that increases after 4 or more years of use.[54] Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.[55-56]

Studies in the United States and Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users.[57-59] However, these cancers are rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than 1 per 1,000,000 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 Aranelle® prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir [*see Contraindications].* Aranelle® 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. 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 women who have used oral contraceptives prior to pregnancy.[60-62] 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.[60,61,63,64]

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

8. Gallbladder Disease

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens.[65-66] More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal.[67] The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.[68]

9. Carbohydrate and Lipid Metabolic Effects

Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users.[25] Oral contraceptives containing greater than 75 mcg of estrogen cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance.[70] Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents.[25, 71] However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose.[69] Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

Some women may develop persistent hypertriglyceridemia while on the pill.[72] As discussed earlier (see **WARNINGS, *Myocardial Infarction and Dose-Related Risk of Vascular Disease from Oral Contraceptives***), changes in serum triglycerides

and lipoprotein levels have been reported in oral contraceptive users.[23]

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.[73, 84] Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations 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 elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs oral contraceptives should be discontinued. 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.[73-75]

11. Headache

The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause.

12. Bleeding Irregularities

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first 3 months of use. Non-hormonal 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, especially when such a condition was pre-existent.

PRECAUTIONS

General

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

1. Physical Examination and Follow-Up

It is good medical practice for all women to have annual history and physical examinations, 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 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.

2. 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.

3. Liver Function

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

4. 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.

5. Emotional Disorders

Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

6. Contact Lenses

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

7. Drug Interactions

Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin. A similar association though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and possibly with griseofulvin, ampicillin and tetracyclines.[76]

Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation

Do not coadminister Aranelle® 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**).

8. 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), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 concentration is unaltered.

c. Other binding proteins may be elevated in serum.

d. Sex steroid binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged.

e. Triglycerides may be increased.

f. Glucose tolerance may be decreased.

g. 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.

9. Carcinogenesis

See **WARNINGS** section.

10. Pregnancy

Pregnancy Category X. See **CONTRAINDICATIONS** and **WARNINGS** sections.

11. Nursing Mothers

Small amounts of oral contraceptive steroids 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, 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 oral contraceptives but to use other forms of contraception until she has completely weaned her child.

12. Pediatric Use

Safety and efficacy of Aranelle® 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 the product before menarche is not indicated.

INFORMATION FOR THE PATIENT

See **PATIENT LABELING** printed below.

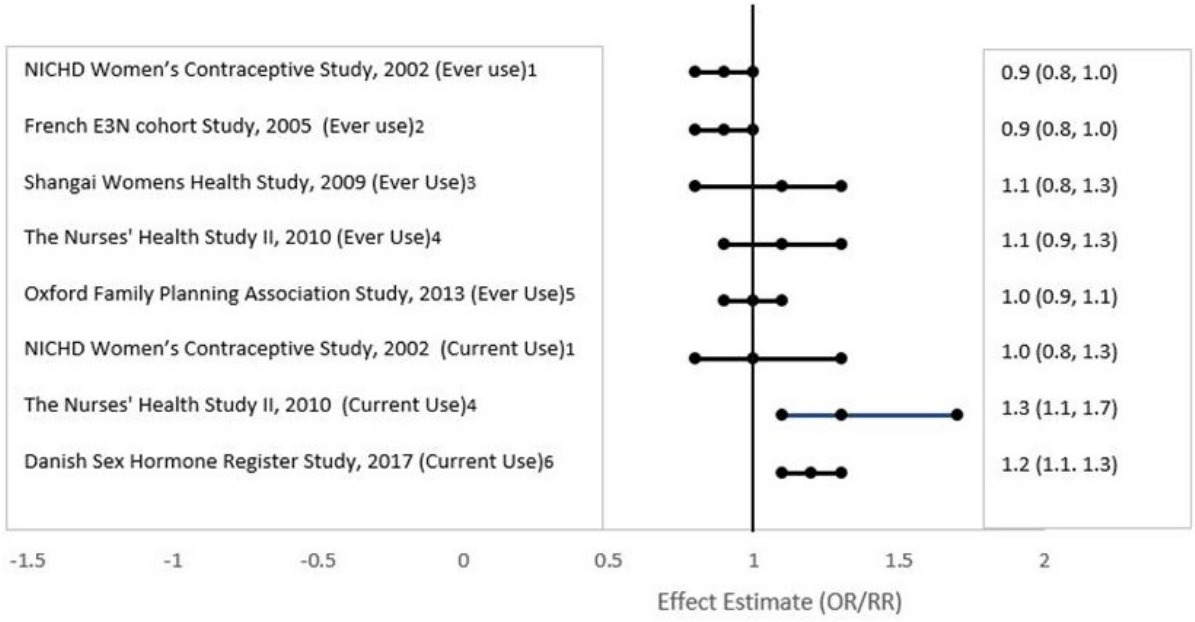
ADVERSE REACTIONS

Post Marketing Experience

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

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

Figure I. Risk of Breast Cancer with Combined Oral Contraceptive Use



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

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

- Thrombophlebitis
- Arterial thromboembolism
- Pulmonary embolism
- Myocardial infarction
- Cerebral hemorrhage
- Cerebral thrombosis
- Hypertension
- Gallbladder disease
- Hepatic adenomas, carcinomas or benign liver tumors

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed:

- Mesenteric thrombosis
- Retinal thrombosis

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

- Nausea
- Vomiting

- Gastrointestinal symptoms (such as abdominal cramps and bloating)
- Breakthrough bleeding
- Spotting
- Change in menstrual flow
- Amenorrhea
- Temporary infertility after discontinuation of treatment
- Edema
- Melasma which may persist
- Breast changes: tenderness, enlargement, secretion
- Change in weight (increase or decrease)
- Change in cervical erosion and secretion
- Diminution in lactation when given immediately postpartum
- Cholestatic jaundice
- Migraine
- Rash (allergic)
- Mental depression
- Reduced tolerance to carbohydrates
- Vaginal candidiasis
- Change in corneal curvature (steepening)
- Intolerance to contact lenses

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

- Pre-menstrual syndrome
- Cataracts
- Changes in appetite
- Cystitis-like syndrome
- Headache
- Nervousness
- Dizziness
- Hirsutism
- Loss of scalp hair
- Erythema multiforme
- Erythema nodosum
- Hemorrhagic eruption
- Vaginitis
- Porphyria
- Impaired renal function
- Hemolytic uremic syndrome
- Budd-Chiari syndrome
- Acne
- Changes in libido
- Colitis

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal

bleeding may occur in females.

NON-CONTRACEPTIVE HEALTH BENEFITS

The following non-contraceptive health benefits related to the use of oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing estrogen doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg of mestranol.[6-11]

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, oral contraceptives must be taken exactly as directed and at intervals not exceeding 24 hours.

For a DAY 1 START, count the first day of menstrual flow as Day 1 and the first light yellow tablet is then taken on Day 1. For a SUNDAY START when menstrual flow begins on or before Sunday, the first light yellow tablet is taken on that day. With either a DAY 1 START or SUNDAY START, 1 light yellow tablet is taken for 7 days, then 1 white tablet for 9 days, then 1 light yellow tablet for 5 days, then 1 peach tablet (inert) for 7 days, whether bleeding has stopped or not. With either a DAY 1 START or SUNDAY START 1 tablet is taken each day at the same time for 28 days. After all 28 tablets are taken, whether bleeding has stopped or not, the same dosage schedule is repeated beginning on the following day.

INSTRUCTIONS TO PATIENTS

- To achieve maximum contraceptive effectiveness, the oral contraceptive pill must be taken exactly as directed and at intervals not exceeding 24 hours.
- Important: Women should be instructed to use an additional method of protection until after the first 7 days of administration *in the initial cycle*.
- Due to the normally increased risk of thromboembolism occurring postpartum, women should be instructed not to initiate treatment with oral contraceptives earlier than 4 weeks after a full-term delivery. If pregnancy is terminated in the first 12 weeks, the patient should be instructed to start oral contraceptives immediately or within 7 days. If pregnancy is terminated after 12 weeks, the patient should be instructed to start oral contraceptives after 2 weeks.[33, 77]

- If spotting or breakthrough bleeding should occur, the patient should continue the medication according to the schedule. Should spotting or breakthrough bleeding persist, the patient should notify her physician.
- If the patient misses 1 pill, she should be instructed to take it as soon as she remembers and then take the next pill at the regular time. The patient should be advised that missing a pill can cause spotting or light bleeding and that she may be a little sick to her stomach on the days she takes the missed pill with her regularly scheduled pill. If the patient has missed more than one pill, see **DETAILED PATIENT LABELING, HOW TO TAKE THE PILL, WHAT TO DO IF YOU MISS PILLS**.
- Use of oral contraceptives in the event of a missed menstrual period:
- If the patient has not adhered to the prescribed dosage regimen, the possibility of pregnancy should be considered after the first missed period and oral contraceptives should
  be withheld until pregnancy has been ruled out.
- If the patient has adhered to the prescribed regimen and misses 2 consecutive periods,
  pregnancy should be ruled out before continuing the contraceptive regimen.

HOW SUPPLIED

Aranelle® - 28-Day Regimen (norethindrone and ethinyl estradiol tablets USP 0.5/0.035 mg and 1/0.035 mg) – Each blister card contains 12 light yellow, round, flat-faced, beveled-edge, unscored tablets, debossed with stylized b on one side and 341 on the other side each containing 0.5 mg norethindrone and 0.035 mg ethinyl estradiol; 9 white, round, flat-faced, beveled-edge, unscored tablets, debossed with stylized b on one side and 342 on the other side each containing 1 mg norethindrone and 0.035 mg ethinyl estradiol; and 7 peach, round, flat-faced, beveled-edge, unscored placebo tablets, debossed with stylized b on one side and 343 on the other side. The first row contains 7 light yellow tablets; the second row contains 7 white tablets; the third row contains 2 white and 5 light yellow tablets and the fourth row contains 7 peach inert tablets.

Available in a box of 3 blister cards (NDC: 0555-9066-67).

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.

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Teva Pharmaceuticals USA, Inc.

North Wales, PA 19454

Rev. C 11/2021

DETAILED PATIENT LABELING

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

INTRODUCTION

Any woman who considers using oral contraceptives ("birth control pills" 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 also will 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 health care 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 regular visits. You also should follow the advice of your health care provider with regard to regular checkups while you are on the pill.

EFFECTIVENESS OF ORAL CONTRACEPTIVES

Oral contraceptives are used to prevent pregnancy and are more effective than other non-surgical methods of birth control. When they are taken correctly, without missing any pills, the chance of becoming pregnant is less than 1% (1 pregnancy per 100 women per year of use). Typical failure rates are actually 3% per year. The chance of becoming pregnant increases with each missed pill during a menstrual cycle.

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

TABLE 1

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 First Year of Use		% of Women Continuing Use at One Year[C]
Method (1)	**Typical Use[A] (2)**	**Perfect Use[B] (3)**	**(4)**
Chance[D]	85	85	
Spermicides[E]	26	6	40
Periodic abstinence	25		63
Calendar		9	
Ovulation method		3	
Sympto-thermal[F]		2	
Post-ovulation		1	
Withdrawal	19	4	
Cap[G]			
Parous women	40	26	42
Nulliparous women	20	9	56
Sponge			
Parous women	40	20	42
Nulliparous women	20	9	56
Diaphragm[G]	20	6	56
Condom[H]			
Female (Reality)	21	5	56

Male	14	3	61
Pill	5		71
Progestin only		0.5	
Combined		0.1	
IUD			
Progesterone T	2	1.5	81
Copper T 380A	0.8	0.6	78
LNg 20	0.1	0.1	81
Depo-Provera	0.3	0.3	70
Norplant and Norplant-2	0.05	0.05	88
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.10	100

Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.[I]

Lactational Amenorrhea Method: LAM is a highly effective, *temporary* method of contraception[J]

Source: Trussell J, Contraceptive Efficacy Table from Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Kowal D, Guest F, *Contraceptive Technology: Seventeenth Revised Edition.* New York, NY: Irvington Publishers, 1998.
(A) 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.
(B) 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.
(C) Among couples attempting to avoid pregnancy, the percentage who continue to use a method for one year.
(D) 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.
(E) Foams, creams, gels, vaginal suppositories, and vaginal film.
(F) Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.
(G) With spermicidal cream or jelly.
(H) Without spermicides.
(I) The treatment schedule is one dose within 72 hours after unprotected intercourse and a second dose 12 hours after the first dose. The Food and Drug Administration has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral (1 dose is 2 white pills), Alesse (1 dose is 5 pink pills), Nordette or Levlen (1 dose is 2 light-orange pills), Lo/Ovral (1 dose is 4 white pills), Triphasil or Tri-Levlen (1 dose is 4 yellow pills).
(J) 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 six months of age.

WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives are strongly advised not to smoke.

Some women should not use the pill. For example, you should not take the pill if you are pregnant or think you may be pregnant. You also should not use the pill if you have any of the following conditions:

- A history of heart attack or stroke
- Blood clots in the legs (thrombophlebitis), brain (stroke), 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
- Unexplained vaginal bleeding (until a diagnosis is reached by your doctor)
- Yellowing of the whites of the eyes or of the skin (jaundice) during pregnancy or during previous use of the pill
- Liver tumor (benign or cancerous)
- Known or suspected pregnancy
- 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.

Tell your health care provider if you have ever had any of these conditions. Your health care provider can recommend a safer method of birth control.

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

Tell your health care provider if you have or have had:

- Breast nodules, fibrocystic disease of the breast, an abnormal breast x-ray or mammogram
- Diabetes
- Elevated cholesterol or triglycerides
- High blood pressure
- Migraine or other headaches or epilepsy
- Mental depression
- Gallbladder, heart or kidney disease
- History of scanty or irregular menstrual periods

Women with any of these conditions should be checked often by their health care provider if they choose to use oral contraceptives.

Also, be sure to inform your doctor or health care provider if you smoke or are on any medications.

RISKS OF TAKING ORAL CONTRACEPTIVES

1. Risk of developing blood clots

Blood clots and blockage of blood vessels are the most serious side effects of taking oral contraceptives. 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.

If you take oral contraceptives and need elective surgery, need to stay in bed for a prolonged illness or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your doctor 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. It is advisable to wait for at least four weeks after delivery if you are not breast feeding. If you are breast feeding, you should wait until you have weaned your child before using the pill (see **GENERAL PRECAUTIONS, While breast feeding)**.

2. Heart attacks and strokes

Oral contraceptives may increase the tendency to develop strokes (stoppage 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 temporary or permanent 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.

3. Gallbladder disease

Oral contraceptive users may have a greater risk than non-users of having gallbladder disease, although this risk may be related to pills containing high doses of estrogen.

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 2 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. Risk of Cancer

It is not known if hormonal birth control pills causes breast cancer. Some studies, but not all, suggest that there could be a slight increase in the risk of breast cancer among current users with longer duration of use.

If you have breast cancer now, or have had it in the past, do not use hormonal birth control because some breast cancers are sensitive to hormones.

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.

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:

ESTIMATED ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NON-STERILE WOMEN, BY FERTILITY CONTROL METHOD ACCORDING TO AGE.

			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[(A)]	7	7.4	9.1	14.8	25.7	28.2
Oral contraceptives						
nonsmoker[(B)]	0.3	0.5	0.9	1.9	13.8	31.6
smoker[(B)]	2.2	3.4	6.6	13.5	51.1	117.2
IUD[(B)]	0.8	0.8	1	1	1.4	1.4
Condom[(A)]	1.1	1.6	0.7	0.2	0.3	0.4

Diaphragm/Spermicide[(A)]	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence[(A)]	2.5	1.6	1.6	1.7	2.9	3.6

(A) Deaths are birth-related

(B) Deaths are method-related

Estimates adapted from H.W. Ory [41]

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 from the table that for women aged 15 to 39 the risk of death is 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 is always lower than that associated with pregnancy for any age group, although over the age of 40 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 4 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 don't smoke should not take oral contraceptives is based on information from older high-dose pills and on less selective use of pills than is practiced today. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of oral contraceptive use by healthy, non-smoking women over 40 years of age may outweigh the possible risks. However, all women, especially older women, are cautioned to use the lowest dose pill that is effective.

WARNING SIGNALS

If any of these adverse effects occur while you are taking oral contraceptives, call your doctor 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 doctor or health care provider to show you how to examine your breasts)
- Severe pain or tenderness in the stomach area (indicating a possible 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. Vaginal bleeding

Irregular vaginal bleeding or spotting may occur while you are taking the pill. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Irregular 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 problem. It is important to continue taking your pills on schedule. If the bleeding occurs in more than 1 cycle or lasts for more than a few days, talk to your doctor or health care provider.

2. Contact lenses

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

4. Melasma (Mask of Pregnancy)

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

5. Other side effects

Other side effects may include change in appetite, headache, nervousness, depression, dizziness, loss of scalp hair, rash and vaginal infections.

If any of these side effects occurs, contact your doctor or health care provider.

GENERAL PRECAUTIONS

1. Missed periods and use of oral contraceptives before or during early pregnancy

At times you may not menstruate regularly after you have completed taking a cycle of pills. If you have taken your pills regularly and miss 1 menstrual period, continue taking your pills for the next cycle but be sure to inform your health care provider before doing so. If you have not taken the pills daily as instructed and miss 1 menstrual period, or if you miss 2 consecutive menstrual periods, you may be pregnant. Check with your health care provider immediately to determine whether you are pregnant. Do not continue to take oral contraceptives until you are sure you are not pregnant, but continue to use another method of birth control.

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 or any other drugs should not be used during pregnancy unless clearly necessary and prescribed by your doctor. You should check with your doctor about risks to your unborn child from any medication taken during pregnancy.

2. While breast feeding

If you are breast feeding, consult your doctor 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 and use another method of contraception while breast feeding. 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); phenylbutazone (Butazolidin is one brand of this drug) and possibly certain antibiotics. You may need to use additional contraception when you take drugs which can make oral contraceptives less effective.

5. 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.
   - 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.
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 doctor or clinic.

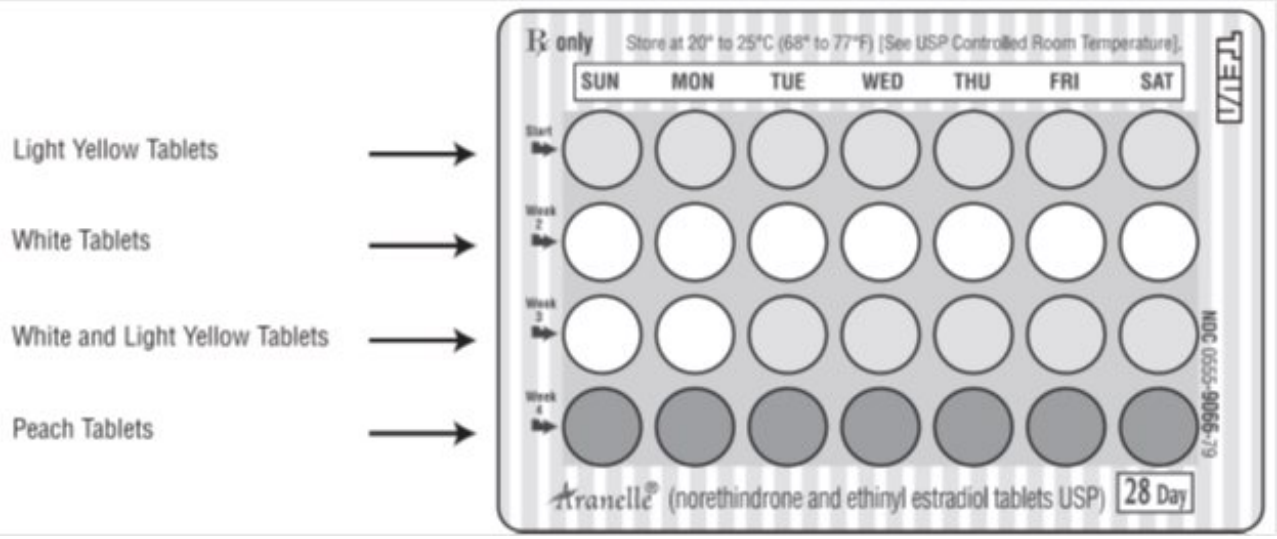
4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills.
   On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.
5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well.
   Use a back-up method (such as condoms, foam, or sponge) until you check with your doctor or clinic.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or clinic 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 doctor or clinic.

<u>BEFORE</u> 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 TO SEE THAT IT HAS 28 PILLS
   The 28-pill pack has 21 “active” light yellow and white pills (with hormones) to take for 3 weeks, followed by 1 week of reminder peach pills (without hormones). To remove a pill, press down on it with your thumb or finger. The tablet will drop through the back of the tablet dispenser. Do not press on the tablet with your thumbnail, fingernail, or any other sharp object.
3. ALSO FIND:
   1) where on the pack to start taking the pills,
   2) in what order to take the pills (follow the arrows) and
   3) the week numbers as shown in the picture below.
   CHECK PICTURE OF THE FOLD-OVER DOSE CARD AND ADDITIONAL INSTRUCTIONS FOR USING THIS PACKAGE AT THE END OF THE BRIEF SUMMARY PATIENT PACKAGE INSERT.

Active pill colors: light yellow and white

Reminder pill color: peach



For use of Days of the Week Sticker, see **WHEN TO START THE FIRST PACK OF PILLS** below.

4. BE SURE YOU HAVE READY AT ALL TIMES:
- ANOTHER KIND OF BIRTH CONTROL (such as condoms, foam, or sponge) to use as a back-up 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 doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

DAY 1 START:
1. Pick the Days of the Week Sticker that starts with the first day of your period. Place this Days of the Week Sticker over the area that has the days of the week (starting with Sunday) pre-printed on the tablet dispenser. Note: if the first day of your period is a Sunday, you can skip step #1.
2. Take the first "active" light yellow pill of the first pack during the first 24 hours of your period.
3. You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

SUNDAY START:
1. Take the first "active" light yellow 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 another method of birth control as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms, foam, or the sponge are good back-up methods of birth control.

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 OR SWITCH YOUR BRAND OF PILLS:**
   - Start the next pack on the day after your last “reminder” pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** light yellow or white “active” pill:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.
2. You do not need to use a back-up birth control method if you have sex.

If you **MISS 2** light yellow or white “active” pills in a row in **WEEK 1 OR WEEK 2** of your pack:

1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

If you **MISS 2** light yellow or white “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 doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

If you **MISS 3 OR MORE** light yellow or white “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 of pills 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 doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

A REMINDER:

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

- THROW AWAY the pills you missed.
- Keep taking 1 pill each day until the pack is empty.
- You do not need a back-up method.

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

- Use a BACK-UP METHOD anytime you have sex.
- KEEP TAKING ONE “ACTIVE” PILL EACH DAY until you can reach your doctor or clinic.

6. Missed periods, spotting or light bleeding

At times, you may not have a period after you have completed a pack of pills. If you miss 1 period but you have taken the pills exactly as you were supposed to, continue as usual into the next cycle. If you have not taken the pills correctly, and have missed a period, you may be pregnant and you should stop taking the pill until your doctor or clinic determines whether or not you are pregnant. Until you can talk to your doctor or clinic, use an appropriate back-up birth control method. If you miss 2 consecutive periods, you should stop taking the pill until it is determined that you are not pregnant.

Even if spotting or light bleeding should occur, continue taking the pill according to the schedule. Should spotting or light bleeding persist, you should notify your doctor or clinic.

7. Stopping the pill before surgery or prolonged bed rest

If you are scheduled for surgery or you need to stay in bed for a long period of time you should tell your doctor that you are on the pill. You should stop taking the pill four weeks before your operation to avoid an increased risk of blood clots. Talk to your doctor about when you may start taking the pill again.

8. Starting the pill after pregnancy

After you have a baby it is advisable to wait 4 to 6 weeks before starting to take the pill. Talk to your doctor about when you may start taking the pill after pregnancy.

9. Pregnancy due to pill failure

When the pill is taken correctly, the expected pregnancy rate is approximately 1% (ie, 1 pregnancy per 100 women per year). If pregnancy occurs while taking the pill, there is little risk to the fetus. The typical failure rate of large numbers of pill users is less than 3% when women who have missed pills are included. If you become pregnant, you should discuss your pregnancy with your doctor.

10. Pregnancy after stopping the pill

There may be some delay in becoming pregnant after you stop taking the pill, especially if you had irregular periods before you started using the pill. Your doctor may recommend that you delay becoming pregnant until you have had one or more regular periods.
There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.

11. Overdosage

There are no reports of serious illness or side effects in young children who have swallowed a large number of pills. In adults, overdosage may cause nausea and/or bleeding in females. In case of overdosage, contact your doctor, clinic or pharmacist.

12. Other information

Your doctor or clinic will take a medical and family history and will examine you before prescribing the pill. The physical examination may be delayed to another time if you request it and the health care provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year. Be sure to inform your doctor or clinic if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your doctor or clinic because this is a time to determine if there are early signs of side effects from using the pill.

Do not use the pill for any condition other than the one for which it was prescribed. The pill has been prescribed specifically for you, do not give it to others who may want birth control pills.
If you want more information about birth control pills, ask your doctor or clinic. They have a more technical leaflet called **PHYSICIAN LABELING** which you might want to read.

NON-CONTRACEPTIVE HEALTH BENEFITS

In addition to preventing pregnancy, use of oral contraceptives may provide certain non-contraceptive health benefits:

- 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
- Ectopic (tubal) pregnancy may occur less frequently
- Non-cancerous 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

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.

BRIEF SUMMARY – PATIENT PACKAGE INSERT

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

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 about 1% per year when used without missing any pills. The typical failure rate of large numbers of pill users is less than 3% per year 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 oral contraceptives 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. The risks associated with taking oral contraceptives increase significantly if you:

- Smoke
- Have high blood pressure, diabetes or high cholesterol
- Have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer of the breast or sex organs, jaundice or malignant or benign liver tumors

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

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives are strongly advised not to 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 3 months of use.

The serious side effects of the pill occur very infrequently, especially if you are in good health and are young. 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) or lungs (pulmonary embolism), stoppage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack or angina pectoris), eye or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences.
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 doctor or health care provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anti-convulsants and some antibiotics, may decrease oral contraceptive effectiveness.

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

Taking the pill provides some important non-contraceptive health 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 health care provider. Your health care 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 health care provider believes that it is a good medical practice 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 health care provider.

HOW TO TAKE THE PILL

See full text of HOW TO TAKE THE PILL which is printed in full in the **DETAILED PATIENT LABELING.**

Call your doctor for medical advice about side effects. You may report side effects to Teva Pharmaceuticals USA, Inc. at 1-866-832-8537 or to FDA at 1-800-FDA-1088.

Teva Pharmaceuticals USA, Inc.

North Wales, PA 19454

Rev. C 11/2021

PRINCIPAL DISPLAY PANEL

NDC 0555-**9066**-67

3 Tablet Dispensers x 28 Tablets

28 DAY REGIMEN

Arnaelle®

(norethindrone and

ethinyl estradiol tablets USP) –

triphasic regimen

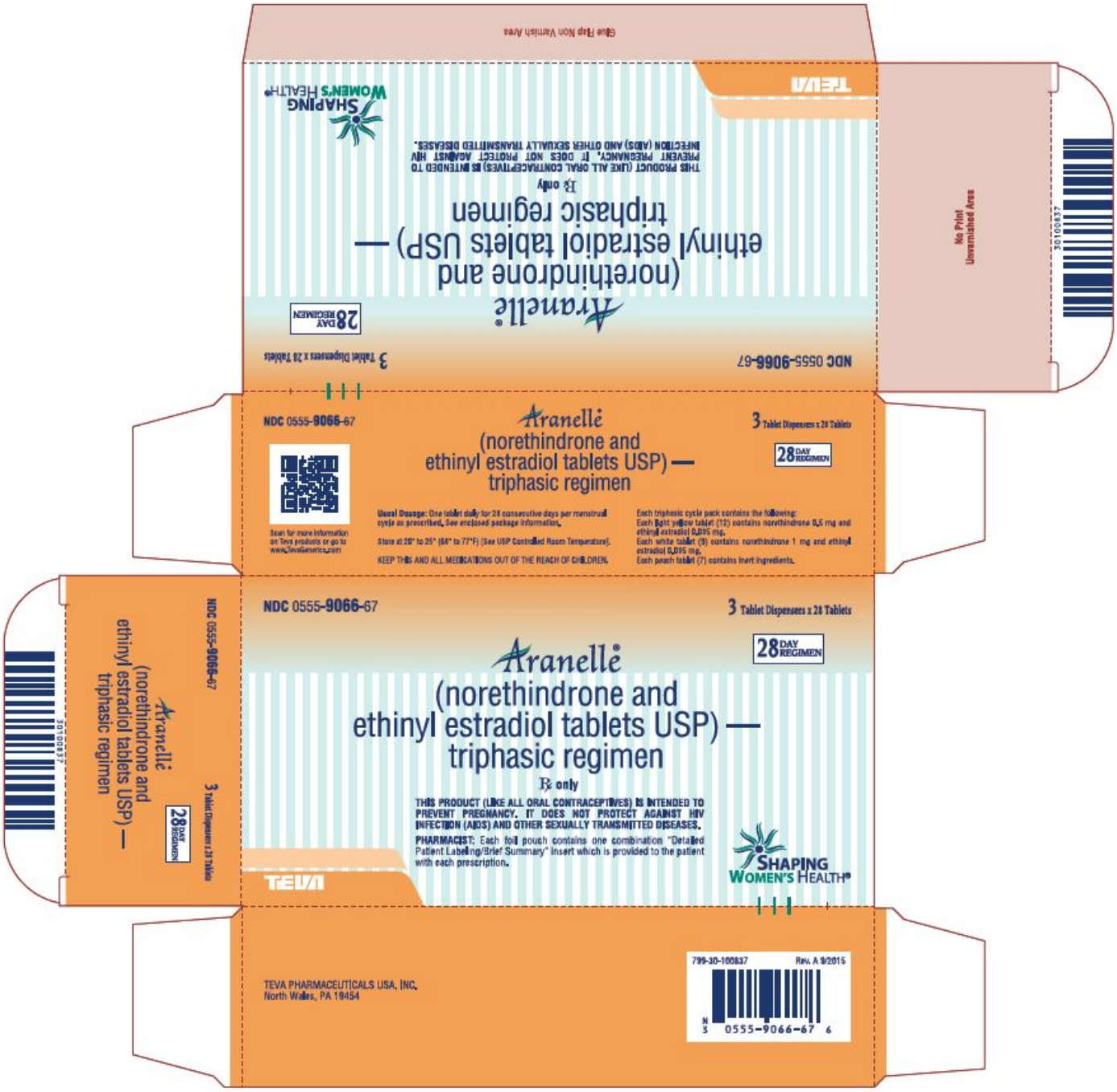
Rx only

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

PHARMACIST: Each foil pouch contains one combination “Detailed Patient Labeling/Brief Summary” insert which is provided to the patient with each prescription.

SHAPING
WOMEN’S HEALTH®

TEVA



ARANELLE

norethindrone and ethinyl estradiol kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0555-9066

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0555-9066-67	3 in 1 CARTON	10/04/2004	

1	NDC:0555-9066-79	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		12
Part 2		9
Part 3		7

Part 1 of 3

ARANELLE

norethindrone and ethinyl estradiol tablet

Product Information

Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NORETHINDRONE (UNII: T18F433X4S) (NORETHINDRONE - UNII:T18F433X4S)	NORETHINDRONE	0.5 mg
ETHINYL ESTRADIOL (UNII: 423D2T571U) (ETHINYL ESTRADIOL - UNII:423D2T571U)	ETHINYL ESTRADIOL	0.035 mg

Inactive Ingredients

Ingredient Name	Strength
D&C YELLOW NO. 10 ALUMINUM LAKE (UNII: CQ3XH3DET6)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
STARCH, CORN (UNII: O8232NY3SJ)	

Product Characteristics

Color	yellow (light yellow)	**Score**	no score
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	b;341
Contains			

Marketing Information

Marketing	Application Number or Monograph	Marketing Start	Marketing End

Category	Citation	Date	Date
ANDA	ANDA076783	10/04/2004	

Part 2 of 3

ARANELLE

norethindrone and ethinyl estradiol tablet

Product Information

Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NORETHINDRONE (UNII: T18F433X4S) (NORETHINDRONE - UNII:T18F433X4S)	NORETHINDRONE	1 mg
ETHINYL ESTRADIOL (UNII: 423D2T571U) (ETHINYL ESTRADIOL - UNII:423D2T571U)	ETHINYL ESTRADIOL	0.035 mg

Inactive Ingredients

Ingredient Name	Strength
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
STARCH, CORN (UNII: O8232NY3SJ)	

Product Characteristics

Color	white	**Score**	no score
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	b;342
Contains			

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076783	10/04/2004	

Part 3 of 3

INERT

inert tablet

Product Information

Route of Administration	ORAL

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
STARCH, CORN (UNII: O8232NY3SJ)	

Product Characteristics

Color	pink (peach)	**Score**	no score
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	b;343
Contains			

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076783	10/04/2004	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076783	10/04/2004	

Labeler - Teva Pharmaceuticals USA, Inc. (001627975)

Revised: 12/2021 Teva Pharmaceuticals USA, Inc.