JOLESSA - levonorgestrel and ethinyl estradiol
Physicians Total Care, Inc.

Rx **only**

11001623
Revised February 2010

Jolessa™ (levonorgestrel / ethinyl estradiol tablets) 0.15 mg / 0.03 mg

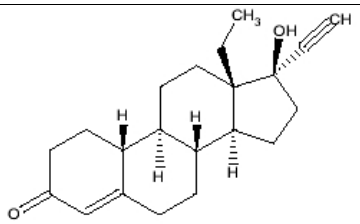
Patients should be counseled that this product does not protect against HIV-infection (AIDS) and other sexually transmitted diseases.

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.

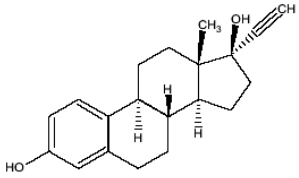
DESCRIPTION

Jolessa™ (levonorgestrel/ethinyl estradiol tablets) is an extended-cycle oral contraceptive consisting of 84 pink active tablets each containing 0.15 mg of levonorgestrel, a synthetic progestogen and 0.03 mg of ethinyl estradiol, and 7 white inert tablets (without hormones).

The chemical formula of levonorgestrel USP is 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17α)-, (-)-, and the chemical formula of ethinyl estradiol USP is 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-. The structural formulas are as follows:



Levonorgestrel
$C_{21}H_{28}O_2$ MW: 312.4



Ethinyl Estradiol
$C_{20}H_{24}O_2$ MW: 296.4

Each pink active tablet contains the following inactive ingredients: anhydrous lactose NF, FD&C blue no. 1, FD&C red no. 40, hydroxypropyl methylcellulose USP, microcrystalline cellulose NF, polyethylene glycol NF, magnesium stearate NF, polysorbate 80 NF, and titanium dioxide USP. Each white inert tablet contains the following inactive ingredients: anhydrous lactose NF, hydroxypropyl methylcellulose USP, microcrystalline cellulose NF, and magnesium stearate NF.

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 changes in the endometrium (which reduce the likelihood of implantation).

PharmacokineticsAbsorption

No specific investigation of the absolute bioavailability of Jolessa™ in humans has been conducted. However, literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability nearly 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 approximately 43%.

Table 1: Mean ± SD Pharmacokinetic Parameters Following A Single Dose Administration of Two Tablets of Jolessa™ in Healthy Female Subjects Under Fasting Conditions

Analyte	**AUC_t (mean ± SD)**	**C_{max} (mean ± SD)**	**T_{max} (mean ± SD)**	**$T_{1/2}$ (mean ± SD)**
Levonorgestrel	60.8 ± 25.6 ng*hr/mL	5.6 ± 1.5 ng/mL	1.4 ± 0.3 hours	29.8 ± 8.3 hours
Ethinyl estradiol	1307 ± 361 pg*hr/mL	145 ± 45 pg/mL	1.6 ± 0.5 hours	15.4 ± 3.2 hours

The effect of food on the rate and the extent of levonorgestrel and ethinyl estradiol absorption following oral administration of Jolessa™ has not been evaluated.

Distribution

The apparent volume of distribution of levonorgestrel and ethinyl estradiol are reported to be approximately 1.8 L/kg and 4.3 L/kg, respectively. Levonorgestrel is about 97.5 - 99% protein-bound, principally to sex hormone binding globulin (SHBG) and, to a lesser extent, serum albumin. Ethinyl estradiol is about 95 - 97% bound to serum albumin. Ethinyl estradiol does not bind to SHBG, but induces SHBG synthesis, which leads to decreased levonorgestrel clearance. Following repeated daily dosing of combination levonorgestrel/ethinyl estradiol oral contraceptives, levonorgestrel plasma concentrations accumulate more than predicted based on single-dose kinetics, due in part, to increased SHBG levels that are induced by ethinyl estradiol, and a possible reduction in hepatic metabolic capacity.

Metabolism

Following absorption, levonorgestrel is conjugated at the 17β-OH position to form sulfate and to a lesser extent, glucuronide conjugates in plasma. Significant amounts of conjugated and unconjugated 3α,5β-tetrahydrolevonorgestrel are also present in plasma, along with much smaller amounts of 3α,5α-tetrahydrolevonorgestrel and 16β-hydroxylevonorgestrel. Levonorgestrel and its phase I metabolites are excreted primarily as glucuronide conjugates. 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.

First-pass metabolism of ethinyl estradiol involves formation of ethinyl estradiol-3-sulfate in the gut wall, followed by 2-hydroxylation of a portion of the remaining untransformed ethinyl estradiol by hepatic cytochrome P-450 3A4 (CYP3A4). Levels of CYP3A4 vary widely among individuals and can explain the variation in rates of ethinyl estradiol hydroxylation. Hydroxylation at the 4-, 6-, and 16-positions may also occur, although to a much lesser extent than 2-hydroxylation. The various hydroxylated metabolites are subject to further methylation and/or conjugation.

Excretion

About 45% of levonorgestrel and its metabolites are excreted in the urine and about 32% are excreted

in feces, mostly as glucuronide conjugates. The terminal elimination half-life for levonorgestrel after a single dose of Jolessa™ was about 30 hours.

Ethinyl estradiol is excreted in the urine and feces as glucuronide and sulfate conjugates, and it undergoes enterohepatic recirculation. The terminal elimination half-life of ethinyl estradiol after a single dose of Jolessa™ was found to be about 15 hours.

SPECIAL POPULATIONS

Race

No formal studies on the effect of race on the pharmacokinetics of Jolessa™ were conducted.

Hepatic Insufficiency

No formal studies have been conducted to evaluate the effect of hepatic disease on the pharmacokinetics of Jolessa™. However, steroid hormones may be poorly metabolized in patients with impaired liver function.

Renal Insufficiency

No formal studies have been conducted to evaluate the effect of renal disease on the pharmacokinetics of Jolessa™.

Drug-Drug Interactions

See PRECAUTIONS section – Drug Interactions.

INDICATIONS AND USAGE

Jolessa™ tablets are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

In a 1-year controlled clinical trial, 4 pregnancies occurred in women 18-35 years of age during 809 completed 91-day cycles of Jolessa™ during which no backup contraception was utilized. This represents an overall use-efficacy (typical user efficacy) pregnancy rate of 1.98 per 100 women-years of use.

Oral contraceptives are highly effective for pregnancy prevention. Table 2 lists the typical unintended 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® Implant System, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

TABLE 2 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*	
Method (1)	Typical Use† (2)	Perfect Use‡ (3)	(4)

Chance§	85	85	
Spermicides¶	26	6	40
Periodic abstinence	25		63
Calendar		9	
Ovulation method		3	
Sympto-thermal #		2	
Post-ovulation		1	
Withdrawal	19	4	
Cap Þ			
Parous women	40	26	42
Nulliparous women	20	9	56
Sponge			
Parous women	40	20	42
Nulliparous women	20	9	56
Diaphragm Þ	20	6	56
Condom ß			
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 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%. à
Lactational Amenorrhea Method: LAM is a highly effective, *temporary* method of contraception. è Source: Trussell J, Contraceptive efficacy. In 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.
*Among couples attempting to avoid pregnancy, the percentage who continue to use a method for one year.†Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an unintended pregnancy during the first year if they do not stop use for any other reason.‡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 unintended pregnancy during the first year if they do not stop use for any other reason.§The percentages of women 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 percentage who would become pregnant within one year among women now relying on reversible methods of contraception if they abandoned contraception altogether.¶Foams, creams, gels, vaginal suppositories and vaginal film.#Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.ÞWith spermicidal cream or

jelly.ßWithout spermicides.àThe 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).èHowever, 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

Oral contraceptives should not be used in women who currently have the following conditions:

- Thrombophlebitis or thromboembolic disorders
- A past history of deep vein thrombophlebitis or thromboembolic disorders
- Cerebrovascular or coronary artery disease (current or history)
- Valvular heart disease with thrombogenic complications
- Uncontrolled hypertension
- Diabetes with vascular involvement
- Headaches with focal neurological symptoms
- Major surgery with prolonged immobilization
- 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 component of this product

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 risk 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. 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 thrombophilias, hypertension, hyperlipidemias, obesity and diabetes.

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 estrogens and progestogens than those in common use today. The effect of longterm 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 a 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

Use of Jolessa™ provides women with more hormonal exposure on a yearly basis than conventional monthly oral contraceptives containing similar strength synthetic estrogens and progestins (an additional 9 weeks per year). While this added exposure may pose an additional risk of thrombotic and thromboembolic disease, studies to date with Jolessa™ have not suggested an increased risk of these disorders.

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 1) among women who use oral contraceptives.

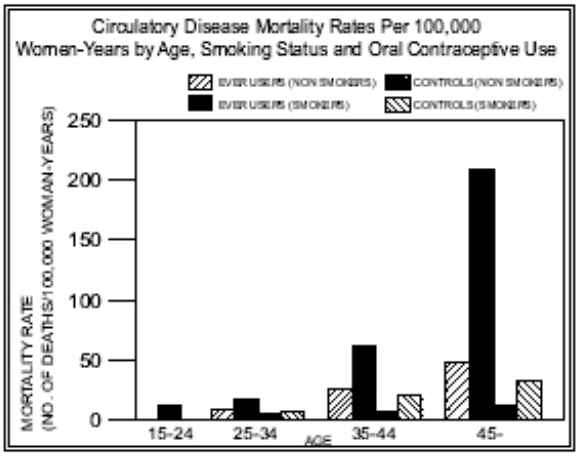


Figure 1 Adapted from P.M. Layde and B Beral, Lancet, 1 :541-546,1981

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 9 in **WARNINGS**). The severity and number of risk factors increase heart disease risk. 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 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 µg ethinyl estradiol) combination oral contraceptives is up to 4 per 10,000 woman-years compared to 0.5-3 per 10,000 woman-years for non-users. However, the incidence is less than that associated with pregnancy (6 per 10,000 woman-years). The risk of thromboembolic disease due to oral contraceptives is not related to length of use

and 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 breast-feed.

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, hyperlipidemias, and obesity. Women with migraine (particularly migraine with aura) 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 old 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 micrograms 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 3). 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.

that is effective.

TABLE 3: 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	AGE 15-19	20-24	25-29	30-34	35-39	40-44
No fertility - control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker†	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

Adapted from H.W. Ory, Family Planning Perpectives, 15:57-63, 1983.
*Deaths are birth related†Deaths are method related

3. Carcinoma of the Reproductive Organs and Breasts

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical cancer in women using oral contraceptives. Although the risk of having breast cancer diagnosed may be slightly increased among current and recent users of combined oral

contraceptives (RR=1.24), this excess risk decreases over time after combination oral contraceptive discontinuation and by 10 years after cessation the increased risk disappears. The risk does not increase with duration of use and no consistent relationships have been found with dose or type of steroid. The patterns of risk are also similar regardless of a woman's reproductive history or her family breast cancer history. The subgroup for whom risk has been found to be significantly elevated is women who first used oral contraceptives before age 20, but because breast cancer is so rare at these young ages, the number of cases attributable to this early oral contraceptive use is extremely small. Breast cancers diagnosed in current or previous oral contraceptive users tend to be less clinically advanced than in never-users. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormone 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 oral contraceptive use and breast cancer 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 their occurrence 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 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. 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.

6. Oral contraceptive Use Before or During Early Pregnancy

Because women using Jolessa™ will likely have withdrawal bleeding only 4 times per year, pregnancy should be ruled out at the time of any missed menstrual period (see **DOSAGE AND ADMINISTRATION** section). Oral contraceptive use should be discontinued if pregnancy is confirmed.

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far 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.

7. Gallbladder Disease

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.

8. 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 micrograms 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** 1a. and 1d.), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

9. Elevated Blood Pressure

Women with significant hypertension should not be started on hormonal contraceptive. 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 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 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.

10. 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**, 1c.)

11. Bleeding Irregularities

When prescribing Jolessa™, the convenience of fewer planned menses (4 per year instead of 13 per year) should be weighed against the inconvenience of increased intermenstrual bleeding and/or spotting.

The clinical trial (SEA 301) that compared the efficacy of Jolessa™ (91-day cycles) to an equivalent dosage 28-day cycle regimen also assessed intermenstrual bleeding. The participants in the study were composed primarily of women who had used oral contraceptives previously as opposed to new users. Women with a history of breakthrough bleeding/spotting ≥10 consecutive days on oral contraceptives were excluded from the study. More Jolessa™ subjects, compared to subjects on the 28-day cycle regimen, discontinued prematurely for unacceptable bleeding (7.7% [Jolessa™] vs. 1.8% [28-day cycle regimen]).

Table 4 shows the percentages of women with ≥ 7 days and ≥ 20 days of intermenstrual spotting and/or bleeding in the Jolessa™ and the 28-day cycle treatment groups.

Table 4. Percentage of Subjects with Intermenstrual Bleeding and/or Spotting

Days of intermenstrual bleeding and/or spotting	Percentage of Subjects*	
Jolessa™	Cycle 1 (N=385)	Cycle 4 (N=261)
≥ 7 days	65%	42%
≥ 20 days	35%	15%
28-day regimen	Cycles 1-4 (N=194)	Cycles 10-13 (N=158)

≥ 7 days	38%	39%
≥ 20 days	6%	4%

*Based on spotting and/or bleeding on days 1-84 of a 91 day cycle in the Jolessa™ subjects and days 1-21 of a 28 day cycle over 4 cycles in the 28-day dosing regimen

Total days of bleeding and/or spotting (withdrawal plus intermenstrual) were similar over one year of treatment for Jolessa™ subjects and subjects on the 28-day cycle regimen.

As in any case of bleeding irregularities, nonhormonal causes should always be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy.

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.

PRECAUTIONS

1. Sexually Transmitted Diseases

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

2. Physical Examination and Follow-up

A periodic history and 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 the 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** 1d.)

In patients with familial defects of lipoprotein metabolism receiving estrogen-containing preparations, there have been case reports of significant elevations of plasma triglycerides leading to pancreatitis.

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

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

7. Contact Lenses

Contact-lens wearers who develop visual changes or changes in lens tolerance should be assessed by

an ophthalmologist.
8. Drug Interactions

Changes in contraceptive effectiveness associated with co-administration of other products
a. Anti-infective agents and anticonvulsants

Contraceptive effectiveness may be reduced when hormonal contraceptives are co-administered 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, barbiturates, phenylbutazone, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate, and griseofulvin. Several cases of contraceptive failure and breakthrough bleeding have been reported in the literature with concomitant administration of antibiotics such as ampicillin and tetracyclines. However, clinical pharmacology studies investigating drug interaction between combined oral contraceptives and these antibiotics have reported inconsistent results.
b. Anti-HIV protease inhibitors

Several of the anti-HIV protease inhibitors have been studied with co-administration of combination oral 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 combination oral contraceptive products may be affected with co-administration 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.
c. Herbal products

Herbal products containing St. John's Wort (hypericum perforatum) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

Increase in plasma levels of estradiol associated with co-administered drugs

Co-administration of atorvastatin and certain combination oral contraceptives containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP 3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

Changes in plasma levels of co-administered drugs

Combination oral contraceptives containing some synthetic estrogens (e.g., ethinyl estradiol) may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporin, prednisolone, and theophylline have been reported with concomitant administration of combination oral contraceptives. Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine and clofibric acid, due to induction of conjugation have been noted when these drugs were administered with combination oral contraceptives. Combination OCs have been shown to significantly decrease plasma concentrations of lamotrigine likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.
9. 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 hormone 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 and levels of various other lipids and lipoproteins may be affected. 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.10. Carcinogenesis

See **WARNINGS** section.
11. Pregnancy

Pregnancy Category X. See **CONTRAINDICATIONS** and **WARNINGS** sections.
12. 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, 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.
13. Pediatric Use

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

Jolessa™ tablets have not been studied in women who have reached menopause.

INFORMATION FOR PATIENT

See Patient Labeling Printed Below.

ADVERSE REACTIONS

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 or benign liver tumors

There is evidence of an association between the following conditions and the use of oral contraceptives:

- 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/fluid retention
- Melasma/chloasma which may persist
- Breast changes: tenderness, enlargement, and secretion
- Change in weight or appetite (increase or decrease)
- Change in cervical ectropion and secretion
- Possible diminution in lactation when given immediately postpartum
- Cholestatic jaundice
- Migraine headache
- Rash (allergic)
- Mood changes, including depression
- Vaginitis, including candidiasis
- Change in corneal curvature (steepening)
- Intolerance to contact lenses
- Decrease in serum folate levels
- Exacerbation of systemic lupus erythematosus
- Exacerbation of porphyria
- Exacerbation of chorea
- Aggravation of varicose veins
- Anaphylactic/anaphylactoid reactions, including urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms

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

- Premenstrual syndrome
- Cataracts
- Optic neuritis which may lead to partial or complete loss of vision
- Cystitis-like syndrome
- Headache
- Nervousness
- Dizziness
- Hirsutism
- Loss of scalp hair
- Erythema multiforme
- Erythema nodosum
- Hemorrhagic eruption
- Impaired renal function
- Hemolytic uremic syndrome
- Budd-Chiari syndrome
- Acne
- Changes in libido
- Colitis
- Pancreatitis
- Dysmenorrhea

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.

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:

- May decrease blood loss and may decrease incidence of iron-deficiency anemia
- May decrease incidence of dysmenorrhea

Effects related to inhibition of ovulation:

- May decrease incidence of functional ovarian cysts
- May decrease incidence of ectopic pregnancies

Effects from long-term use:

- May decrease incidence of fibroadenomas and fibrocystic disease of the breast
- May decrease incidence of acute pelvic inflammatory disease
- May decrease incidence of endometrial cancer
- May decrease incidence of ovarian cancer

DOSAGE AND ADMINISTRATION

Although the occurrence of pregnancy is unlikely if Jolessa™ is taken according to directions, if withdrawal bleeding does not occur while taking white (inactive) tablets, the possibility of pregnancy must be considered. Appropriate diagnostic measures to rule out pregnancy should be taken at the time of any missed menstrual period. Jolessa™ should be discontinued if pregnancy is confirmed.

The dosage of Jolessa™ is one pink (active) tablet daily for 84 consecutive days, followed by 7 days of white (inert) tablets. To achieve maximum contraceptive effectiveness, Jolessa™ must be taken exactly as directed and at intervals not exceeding 24 hours. Ideally, the tablets should be taken at the same time of the day on each day of active treatment. The tablets should not be removed from the protective blister packaging to avoid damage to the product. The dispenser card should be kept in the foil pouch until dispensed to the patient.

During the first cycle of medication, the patient is instructed to begin taking Jolessa™ on the first Sunday after the onset of menstruation. If menstruation begins on a Sunday, the first tablet (pink) is taken that day. One pink tablet should be taken daily for 84 consecutive days, followed by 7 days on which a white (inert) tablet is taken. Withdrawal bleeding should occur during the 7 days following discontinuation of pink active tablets. During the first cycle, contraceptive reliance should not be placed on Jolessa™ until a pink (active) tablet has been taken daily for 7 consecutive days and a non-hormonal back-up method of birth control (such as condoms or spermicide) should be used during those 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

The patient begins her next and all subsequent 91-day courses of tablets without interruption on the same day of the week (Sunday) on which she began her first course, following the same schedule: 84 days on which pink tablets are taken followed by 7 days on which white tablets are taken. If in any cycle the patient starts tablets later than the proper day, she should protect herself against pregnancy by using a non-hormonal back-up method of birth control until she has taken a pink tablet daily for 7 consecutive days.

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

For patient instructions regarding missed pills, see the "**WHAT TO DO IF YOU MISS PILLS**" section in the **DETAILED PATIENT LABELING**. Any time the patient misses two or more pink tablets, she should also use another method of nonhormonal back-up contraception until she has taken a pink tablet daily for seven consecutive days. If the patient misses one or more white tablets, she is still protected against pregnancy provided she begins taking pink tablets again on the proper day. The possibility of ovulation increases with each successive day that scheduled pink tablets are missed. The risk of pregnancy increases with each active (pink) tablet missed.

In the nonlactating mother, Jolessa™ may be initiated no earlier than day 28 postpartum, for contraception due to the increased risk for thromboembolism. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered (See **CONTRAINDICATIONS**, **WARNINGS** and **PRECAUTIONS** concerning thromboembolic disease). The patient should be advised to use a nonhormonal back-up method for the first 7 days of tablet-taking. However, if intercourse has already occurred, the possibility of ovulation and conception prior to initiation of medication should be considered. Jolessa™ may be initiated immediately after a first-trimester abortion; if the patient starts Jolessa™ immediately, additional contraceptive measures are not needed.

HOW SUPPLIED

Jolessa™ tablets (levonorgestrel / ethinyl estradiol tablets) 0.15 mg / 0.03 mg are available in Extended-Cycle Tablet Dispensers, each containing a 13-week supply of tablets: 84 pink tablets, each containing 0.15 mg of levonorgestrel and 0.03 mg ethinyl estradiol, and 7 white inert tablets. The active pink tablets are round, film-coated, unscored, debossed with **stylized b** on one side and **992** on the other side. The white inert tablets are round, unscored, debossed with **stylized b** on one side and **208** on the other side.

Available in dispenser of 91 tablets	NDC 54868-6044-0

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

References available upon request.

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 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). The typical failure rate of pill users is approximately 5% per year when women who miss pills are included.

For the majority of women, oral contraceptives can be taken safely. But for some women oral contraceptive use is associated with 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 are obese
- 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 are pregnant.

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 also greater potential health risks associated with pregnancy in older women.

Cigarette smoking increases the risk of serious cardiovascular side effects 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 are nausea, vomiting, bleeding or spotting between menstrual periods, weight gain, breast tenderness, and difficulty wearing contact lenses. Some of 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 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), 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) 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 when taking the pill.
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 patient information leaflet. 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, and herbal preparations containing St. John's Wort (hypericum perforatum) may decrease oral contraceptive effectiveness.

Breast cancer has been diagnosed slightly more often in women who use the pill than in women of the same age who do not use the pill. This very small increase in the number of breast cancer diagnoses gradually disappears during the 10 years after stopping use of the pill. It is not known whether the difference is caused by the pill. It maybe 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 hormonal contraceptives because breast cancer is usually a hormone-sensitive tumor.

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

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.

What You Should Know About Your Menstrual Cycle When Taking Jolessa™

When you take Jolessa™, which has a 91-day treatment cycle, you should expect to have 4 menstrual

periods per year (bleeding when you are taking the 7 white pills). However, you also should expect to have more bleeding or spotting between your menstrual periods than if you were taking an oral contraceptive with a 28-day treatment cycle. During the first Jolessa™ treatment cycle, about 1 in 3 women may have 20 or more days of unplanned bleeding or spotting (bleeding when you are taking pink pills). This bleeding or spotting tends to decrease during later cycles. Do not stop Jolessa™ because of the bleeding. If the spotting continues for more than 7 consecutive days or if the bleeding is heavy, call your healthcare provider.

If You Miss Your Menstrual Period When Taking Jolessa™

You should consider the possibility that you are pregnant if you miss your menstrual period (no bleeding on the days that you are taking white tablets). Since scheduled menstrual periods are less frequent when you are taking Jolessa™, notify your healthcare provider that you have missed your period and are taking Jolessa™. Also notify your healthcare provider if you have symptoms of pregnancy such as morning sickness or unusual breast tenderness. It is important that your healthcare provider evaluates you to determine if you are pregnant. Stop taking Jolessa™ if it is determined that you are pregnant.

HOW TO TAKE JOLESSA™

IMPORTANT POINTS TO REMEMBER *BEFORE* YOU START TAKING JOLESSA™

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 JOLESSA™ 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 MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST FEW WEEKS OF TAKING 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. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING DURING THE FIRST FEW MONTHS OF TAKING JOLESSA™. **Do not stop taking your pills even if you are having irregular bleeding**. If the bleeding lasts for more than 7 consecutive days, talk to your healthcare provider.
5. 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.
6. IF YOU HAVE VOMITING OR DIARRHEA, or IF YOU TAKE SOME MEDICINES, including some antibiotics and the herbal supplement St. John's Wort, Jolessa™ may not work as well. Use a back-up method (such as condoms or spermicides) until you check with your healthcare provider.
7. IF YOU HAVE TROUBLE REMEMBERING TO TAKE JOLESSA™, talk to your healthcare provider about how to make pill-taking easier or about using another method of birth control.
8. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your healthcare provider.

***BEFORE* YOU START TAKING JOLESSA™**

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 EXTENDED-CYCLE TABLET DISPENSER. Your Tablet Dispenser consists of 3 trays with cards that hold 91 individually sealed pills (a 13-week or 91-day cycle). The 91 pills consist of 84 pink pills (active pills with hormones) and 7 white pills, (inactive pills without hormone). Trays 1 and 2 each contain 28 pink pills (4 rows of 7 pills). Tray 3 contains 35 pills

consisting of 28 pinks pills (4 rows of 7 pills) and 7 white pills (1 row of 7 pills).

3. ALSO FIND:
   • Where on the first row in the pack to start taking pills (upper left corner at the start arrow) and
   • In what order to take the pills (follow the weeks and arrow).
4. BE SURE YOU HAVE READY AT ALL TIMES ANOTHER KIND OF BIRTH CONTROL (such as condoms or spermicides), to use as a back-up in case you miss pills.

WHEN TO START JOLESSA™

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

HOW TO TAKE JOLESSA™

1. Take one pill at the same time every day until you have taken the last pill in the tablet dispenser. Do not skip pills even if you are spotting or bleeding 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 TABLET DISPENSER.
   After taking the last white pill, start taking the first pink pill from a new Extended-Cycle Tablet Dispenser the very next day regardless of when your period started. This should be on a Sunday.
3. If you miss your period when you are taking the white pills, call your healthcare provider because you may be pregnant.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** pink "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** pink "active" pills in a row:

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 another birth control method (such as condoms or spermicide) as a back-up on the 7 days after you restart your pills.

If you **MISS 3 OR MORE** pink "active" pills in a row:

1. Do not remove the missed pills from the pack as they will not be taken. Keep taking 1 pill every day as indicated on the pack until you have completed all of the remaining pills in the pack. For example: If you resume taking the pill on Thursday, take the pill under "Thursday" and do not take the missed pills. You may experience bleeding during the week following the missed pills.
2. You COULD BECOME PREGNANT if you have sex during the days of missed pills or during the first 7 days after restarting your pills.
3. You **must** use a non-hormonal birth control method (such as condoms or spermicide) as a back-up when you miss pills and for the first 7 days after you restart your pills. **If you miss your period when taking the white pills, call your healthcare provider because you may be pregnant**.

If you **MISS ANY** of the 7 white inactive pills.

1. Throw away the missed pills.
2. Keep taking the scheduled pills until the pack is finished.
3. You do not need a back-up method of birth control.

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

1. Use a BACK-UP METHOD anytime you have sex.
2. KEEP TAKING ONE PILL EACH DAY until you contact your healthcare provider.

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 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. Although oral contraceptives have important advantages over other methods of contraception, they have certain risks that no other method has, and some of these risks may continue after you have stopped using the oral contraceptive. 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 Jolessa™ 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 your healthcare provider, both when you first start taking Jolessa™ and during your revisits. You should also follow your healthcare provider's advice with regard to regular check-ups while you are on Jolessa™.

EFFECTIVENESS OF ORAL CONTRACEPTIVES

Oral contraceptives or "the birth control pill" or "the pill" are used to prevent pregnancy and are more effective than most other nonsurgical methods of birth control. The chance of becoming pregnant is approximately 1.0% per year (1 pregnancy per 100 women per year of use) when the pills are used correctly, and no pills are missed. Typical failure rates are approximately 5.0% per year when women who miss pills are included. The chance of becoming pregnant increases with each missed pill during the menstrual cycle.

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

No methods: 85%

Vaginal sponge: 20 to 40%

Cervical cap: 20 to 40%

Spermicides alone: 26%

Periodic abstinence: 25%

Condom (female): 21%

Diaphragm with spermicides: 20%

Withdrawal: 19%

Condom (male): 14%

Female sterilization: 0.5%

IUD: 0.1 to 2.0%

Injectable progestogen: 0.3%

Male sterilization: 0.15%

Norplant system: 0.05%

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 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. You should not use the pill if you have any of the following conditions:

- A history of heart attack or stroke
- A history of 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, vagina, or certain hormonally-sensitive cancers
- Unexplained vaginal bleeding (until a diagnosis is reached by your healthcare provider)
- 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
- Heart valve or heart rhythm disorders that may be associated with formation of blood clots
- Diabetes affecting your circulation
- Uncontrolled high blood pressure
- Active liver disease with abnormal liver function tests
- Allergy or hypersensitivity to any of the components of Jolessa™
- A need for surgery with prolonged bedrest

Tell your healthcare provider if you have any of the above conditions. Your healthcare provider can recommend a safer method of birth control.

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
- 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.

RISKS OF TAKING ORAL CONTRACEPTIVES

If you use Jolessa™ you will receive more exposure to hormones on a yearly basis than if you used a conventional 28-day cycle oral contraceptives containing a similar amount of estrogen and progestin (an additional 9 weeks exposure per year). While this added exposure may pose an additional risk of thrombotic and thromboembolic disease, studies to date with Jolessa™ have not suggested an increased risk of these disorders.

1. **Risk 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.

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 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. 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 on **Breastfeeding** in "**GENERAL PRECAUTIONS**.")

The risk of circulatory disease in oral contraceptive users may be higher in users of high-dose pills (containing 50 micrograms or higher of ethinyl estradiol) and may be greater with longer duration of oral contraceptive use. In addition, some of these increased risks may continue for a number of years after stopping oral contraceptives. The risk of abnormal blood clotting increases with age in both users and nonusers of oral contraceptives, but the increased risk from the oral contraceptive appears to be present at all ages. For women aged 20 to 44, it is estimated that about 1 in 2,000 using oral contraceptives will be hospitalized each year because of abnormal clotting.

Among nonusers in the same age group, about 1 in 20,000 would be hospitalized each year. For oral contraceptive users in general, it has been estimated that in women between the ages of 15 and 34 the risk of death due to a circulatory disorder is about 1 in 12,000 per year, whereas for nonusers the rate is about 1 in 50,000 per year. In the age group 35 to 44, the risk is estimated to be about 1 in 2,500 per year for oral contraceptive users and about 1 in 10,000 per year for nonusers.

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 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 with aura) who take oral contraceptives also may be at higher risk of stroke.

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.

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 in general are extremely rare and the chance of developing liver cancer from using the pill is thus even rarer.

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

Breast cancer has been diagnosed slightly more often in women who use the pill than in women of the same age who do not use the pill. This small increase in the number of breast cancer diagnoses gradually disappears during the 10 years after stopping use of the pill. It is not known whether the difference is caused by the pill. It may be that women taking the pill are examined more often, so that breast cancer is 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 or precancerous lesions of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives. There is insufficient evidence to rule out the possibility that the pill may cause such cancers.

6. **Lipid Metabolism and Inflammation of the Pancreas**

In patients with inherited defects of the lipid metabolism, there have been reports of significant elevations of plasma triglycerides during estrogen therapy. This has led to 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

AGE						
Method of control and	15-19	20-24	25-29	30-34	35-39	40-44

outcome						
No fertility - control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker†	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, 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 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 don't 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 that contains the least amount of estrogen and progestin 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 doctor or 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

In addition to the risks and more serious side effects discussed above (see **RISKS OF TAKING ORAL CONTRACEPTIVES, ESTIMATED RISK OF DEATH FROM A BIRTH CONTROL METHOD OR PREGNANCY** and **WARNING SIGNALS** sections), the following may also occur:

1. **Irregular vaginal bleeding**

Irregular vaginal bleeding or spotting (bleeding or spotting between your expected period) is likely to occur while you are taking Jolessa™. 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 91-day cycles of Jolessa™ use, tends to decrease during later cycles, but may also occur after you have been taking Jolessa™ for some time. Such bleeding usually does not indicate any serious problems. **It is important to continue taking your pills on schedule even if you are having irregular bleeding**. If the bleeding lasts for more than 7 consecutive days, talk to your healthcare provider.

When you take Jolessa™, you need to consider the convenience of fewer expected menstrual periods (4 per year instead of 13) and the inconvenience of more irregular vaginal bleeding or spotting. In a clinical trial comparing Jolessa™ (91-day cycles) to a conventional equivalent dosage 28-day cycle oral contraceptive, more women using Jolessa™ discontinued treatment because of bleeding problems (7.7% of the Jolessa™ users compared to 1.8% of the 28-day cycle users).

The following Table shows the percentages of women with 7 or more and 20 or more days of intermenstrual bleeding and/or spotting in the Jolessa™ and the 28-day cycle treatment groups.

Percentages (%) of Women with Intermenstrual Bleeding and/or Spotting

Number of days of intermenstrual bleeding and/or spotting	Percentage of subjects with intermenstrual bleeding or spotting*	
Jolessa™	Cycle 1	Cycle 4
7 or more days	65%	42%
20 or more days	35%	15%
28-day cycle pill	Cycles 1-4	Cycles 10-13
7 or more	38%	39%
20 or more days	6%	4%

*Based on spotting and/or bleeding on days 1-84 of a 91 day cycle in the Jolessa™ subjects and days 1-21 of a 28 day cycle over 4 cycles in the 28-day dosing regimen.

Total days of bleeding and/or spotting (withdrawal plus intermenstrual) were similar over one year of treatment for Jolessa™ subjects and subjects on the 28-day cycle regimen.

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 and vomiting, change in appetite, breast tenderness, headache, nervousness, depression, dizziness, loss of scalp hair, rash, vaginal infections, 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**

If you miss any periods (no bleeding on the days that you take white pills), you must consider the possibility that you may be pregnant. Notify your healthcare provider that you are taking Jolessa™ and have missed your period. Also notify your healthcare provider if you have any symptoms of pregnancy such as morning sickness or unusual breast tenderness. Because you are taking Jolessa™, it is very important that your healthcare provider evaluates you to determine if you are pregnant. Stop taking Jolessa™ 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 breast-feed 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 healthcare provider 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), carbamazepine (Tegretol is one brand of this drug), and phenytoin (Dilantin® is one brand of this drug), primidone (Mysoline®), topiramate (Topamax®), phenylbutazone (Butazolidin® is one brand), some drugs used for HIV such as ritonavir (Norvir®), modafinil (Provigil®) and possibly certain antibiotics (such as ampicillin and other penicillins, and tetracyclines). Pregnancies and breakthrough bleeding have been reported by users of combined hormonal contraceptives who also used some form of the herbal supplement St. John's Wort. You may need to use a non-hormonal method of contraception during any cycle in which you take drugs that can make oral contraceptives less effective. Be sure to tell your healthcare provider if you are taking or start taking any other medications, including nonprescription products or herbal products while taking birth control pills.

You may be at higher risk of a specific type of liver dysfunction if you take troleandomycin and oral

contraceptives at the same time.

Birth control pills may interact with lamotrigine, an anticonvulsant used for epilepsy. This may increase the risk of seizures, so your physician may need to adjust the dose of lamotrigine.

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.

What You Should Know About Your Menstrual Cycle When Taking Jolessa™

When you take Jolessa™, which has a 91-day treatment cycle, you should expect to have 4 menstrual periods per year (bleeding when you are taking the 7 white pills). However, you also should expect to have more bleeding or spotting between your menstrual periods than if you were taking an oral contraceptive with a 28-day treatment cycle. During the first Jolessa™ treatment cycle, about 1 in 3 women may have 20 or more days of unplanned bleeding or spotting (bleeding when you are taking pink pills). This bleeding or spotting tends to decrease during later cycles. Do not stop Jolessa™ because of the bleeding. If the spotting continues for more than 7 consecutive days or if the bleeding is heavy, call your healthcare provider.

HOW TO TAKE JOLESSA™

IMPORTANT POINTS TO REMEMBER *BEFORE* YOU START TAKING JOLESSA™

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 JOLESSA™ 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 MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST FEW WEEKS OF TAKING 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. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING DURING THE FIRST FEW MONTHS OF TAKING JOLESSA™. **Do not stop taking your pills even if you are having irregular bleeding**. If the bleeding lasts for more than a few days, talk to your healthcare provider.
5. 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.
6. IF YOU HAVE VOMITING OR DIARRHEA, or IF YOU TAKE SOME MEDICINES, including some antibiotics and the herbal supplement St. John's Wort, Jolessa™ may not work as well. Use a back-up method (such as condoms or spermicides) until you check with your healthcare provider.
7. IF YOU HAVE TROUBLE REMEMBERING TO TAKE JOLESSA™, talk to your healthcare provider about how to make pill-taking easier or about using another method of birth control.
8. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your healthcare provider.

***BEFORE* YOU START TAKING JOLESSA™**

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 EXTENDED-CYCLE TABLET DISPENSER. Your Tablet Dispenser consists of 3 trays with cards that hold 91 individually sealed pills (a 13-week or 91-day cycle). The 91 pills

consist of 84 pink pills (active pills with hormones) and 7 white pills, (inactive pills without hormone). Trays 1 and 2 each contain 28 pink pills (4 rows of 7 pills). Tray 3 contains 35 pills consisting of 28 pinks pills (4 rows of 7 pills) and 7 white pills (1 row of 7 pills).

3. ALSO FIND:
   • Where on the first row in the pack to start taking pills (upper left corner at the start arrow) and
   • In what order to take the pills (follow the weeks and arrow).
4. BE SURE YOU HAVE READY AT ALL TIMES ANOTHER KIND OF BIRTH CONTROL (such as condoms or spermicides), to use as a back-up in case you miss pills.

WHEN TO START JOLESSA™

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

HOW TO TAKE JOLESSA™

1. **Take one pill at the same time every day until you have taken the last pill in the tablet dispenser.**
   Do not skip pills even if you are spotting or bleeding 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 TABLET DISPENSER.**
   After taking the last white pill, start taking the first pink pill from a new Extended-Cycle Tablet Dispenser **the very next day** regardless of when your period started. This should be on a Sunday.
3. **If you miss your period when you are taking the white pills, call your healthcare provider because you may be pregnant**.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** pink "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** pink "active" pills in a row:

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 another birth control method (such as condoms or spermicide) as a back-up on the 7 days after you restart your pills.

If you **MISS 3 OR MORE** pink "active" pills in a row:

1. Do not remove the missed pills from the pack as they will not be taken. Keep taking 1 pill every day as indicated on the pack until you have completed all of the remaining pills in the pack. For example: If you resume taking the pill on Thursday, take the pill under "Thursday" and do not take the missed pills. You may experience bleeding during the week following the missed pills.
2. You COULD BECOME PREGNANT if you have sex during the days of missed pills or during the first 7 days after restarting your pills.
3. You **must** use a non-hormonal birth control method (such as condoms or spermicide) as a back-up when you miss pills and for the first 7 days after you restart your pills. **If you miss your period when taking the white pills, call your healthcare provider because you may be pregnant.**

If you **MISS ANY** of the 7 white inactive pills.

1. Throw away the missed pills.
2. Keep taking the scheduled pills until the pack is finished.
3. You do not need a back-up method of birth control.

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

1. Use a BACK-UP METHOD anytime you have sex.
2. KEEP TAKING ONE PILL EACH DAY until you contact your healthcare provider.

PREGNANCY DUE TO PILL FAILURE

If taken every day as directed, the incidence of pill failure resulting in pregnancy is approximately 1% (ie, one pregnancy per 100 women per year), but more typical failure rates are about 5%. If failure does occur, the risk to the fetus is minimal.

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.

OVERDOSAGE

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

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:

- May decrease blood loss and may decrease incidence of iron-deficiency anemia
- May decrease incidence of dysmenorrhea

Effects related to inhibition of ovulation:

- May decrease incidence of functional ovarian cysts
- May decrease incidence of ectopic pregnancies

Effects from long-term use:

- May decrease incidence of fibroadenomas and fibrocystic disease of the breast
- May decrease incidence of acute pelvic inflammatory disease
- May decrease incidence of endometrial cancer
- May decrease incidence of ovarian cancer

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

BARR LABORATORIES, INC.

Pomona, NY 10970

Revised February 2010

11001623

Relabeling of Additional barcode label by:

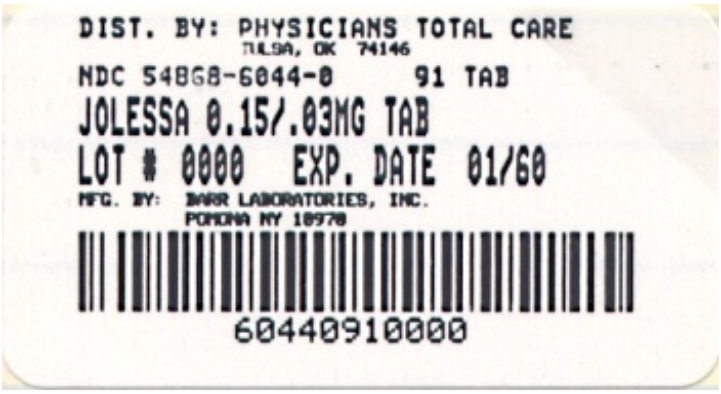
Physicians Total Care, Inc.
Tulsa, OK 74146

PRINCIPAL DISPLAY PANEL

1 Extended-Cycle Tablet Dispensers

91 Tablets Each 91 DAY REGIMEN

NDC 54868-6044-0



Jolessa™
(levonorgestrel / ethinyl estradiol tablets) 0.15 mg/0.03 mg

Contains 1 Extended-Cycle Tablet Dispensers, each containing 91 tablets: 84 pink tablets, each containing 0.15 mg levonorgestrel with 0.03 mg ethinyl estradiol, and 7 white inert tablets.

Rx only

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

Usual Dosage: One tablet daily for 91 consecutive days in the following order: 84 pink tablets followed by 7 white tablets as prescribed.

See enclosed package brochure.

Pharmacist: Dispense patient information with each prescription.

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

JOLESSA

levonorgestrel and ethinyl estradiol kit

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:54868-6044(NDC:0555-9123)

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:54868-6044-0	1 in 1 POUCH		
1		1 in 1 BLISTER PACK		

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1		84
Part 2		7

Part 1 of 2

JOLESSA

levonorgestrel and ethinyl estradiol tablet

Product Information	
Route of Administration	ORAL

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
LEVONORGESTREL (UNII: 5W7SIA7YZW) (LEVONORGESTREL - UNII:5W7SIA7YZW)	LEVONORGESTREL	0.15 mg
ETHINYL ESTRADIOL (UNII: 423D2T571U) (ETHINYL ESTRADIOL - UNII:423D2T571U)	ETHINYL ESTRADIOL	0.03 mg

Inactive Ingredients	
Ingredient Name	**Strength**
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
HYPROMELLOSE 2208 (15000 MPA.S) (UNII: Z78RG6M2N2)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POLYETHYLENE GLYCOL (UNII: 3WJQ0SDW1A)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics			
Color	pink	**Score**	no score
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	b;992
Contains			

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021544	06/24/2009	

Part 2 of 2

INERT

inert tablet

Product Information	
Route of Administration	ORAL

Inactive Ingredients	
Ingredient Name	**Strength**
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
HYPROMELLOSE 2208 (15000 MPA.S) (UNII: Z78RG6M2N2)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	

Product Characteristics			
Color	white	**Score**	no score
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	b;208
Contains			

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021544	06/24/2009	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021544	06/24/2009	

Labeler - Physicians Total Care, Inc. (194123980)

Establishment

Name	Address	ID/FEI	Business Operations
Physicians Total Care, Inc.		194123980	relabel

Revised: 1/2011 Physicians Total Care, Inc.