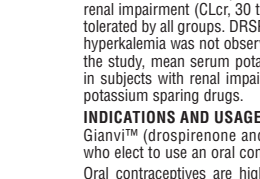




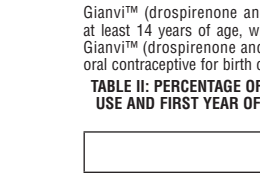
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**DESCRIPTION**  
Gianvi™ (drospirenone and ethinyl estradiol tablets) 3 mg/0.02 mg provides an oral contraceptive regimen consisting of 24 active film-coated tablets each containing 3 mg of drospirenone and 0.02 mg of ethinyl estradiol, 4 inert film-coated tablets containing placebo, cyproterone, FD&C red #40 aluminum lake, FD&C yellow no. 6 aluminum lake, hypromellose, magnesium stearate, polyethylene glycol, polysorbate 80, povidone, pregelatinized starch and titanium dioxide. The inert tablets contain anhydrous lactose, hypromellose, magnesium stearate, croscarmellose cellulose.

**Drospirenone** (ER, 7R, 8S, 10R, 13S, 14S, 15S, 16S, 17S)-3',4',6',6'-tetrahydro-7,8,10,11,12,13,14,15,16,16-hexa-decahydro-10,13-dimethylspiro-[17H-cyclopent[a]phenanthrene-17,2-(5H)-furan]-3,5-(2H)-dione) is a synthetic progestational compound. Ethinyl estradiol (19-nor-17-pregna-1,3,5(10H)-triene-20-yne-3, 17-diol) is a synthetic estrogen. The structural formulas are as follows:



Ethinyl Estradiol



**Pharmacokinetics**  
Oral Contraception  
Combined oral contraceptives (COCs) 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 increases the difficulty of sperm entry into the uterus) and the endometrium (which reduces the likelihood of implantation).

Drospirenone is a spironolactone analogue with antihypertensive activity. Preclinical studies in animals and *in vitro* have shown that drospirenone has no androgenic, estrogenic, glucocorticoid, or anti-glucocorticoid activity. Preclinical studies in animals have also shown that drospirenone has antiandrogenic activity.

**Acne**  
Acne vulgaris is a skin condition with a multifactorial etiology including androgen stimulation of sebaceous production. While the combination of ethinyl estradiol and drospirenone increases sex hormone binding globulin (SHBG) and decreases free testosterone, the relationship between these changes and a decrease in the severity of facial acne in otherwise healthy women with skin condition has not been established. The impact of the androgenic activity of drospirenone on acne is not known.

**Pharmacokinetics**  
**Absorption**  
The absolute bioavailability of drospirenone (DRSP) from a single entity tablet is about 76%. The absolute bioavailability of ethinyl estradiol (EE) is approximately 40% as a result of presystemic conjugation and first-pass metabolism. The absolute bioavailability of drospirenone and ethinyl estradiol tablets, which is a combination tablet of drospirenone and ethinyl estradiol stabilized by betadex as a chelate (molecular inclusion complex), has not been evaluated. The bioavailability of EE is similar when dosed via a betadex chelate formulation compared to when it is dosed as a free steroid. Serum concentrations of DRSP and EE reached peak levels within 1 to 2 hours after administration of drospirenone and ethinyl estradiol tablets.

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For EE, steady-state conditions are reported during the second half of a treatment cycle. Following daily administration of drospirenone and ethinyl estradiol tablets serum C<sub>max</sub> and AUC (0-24h) values of EE accumulated by a factor of about 1.5 to 2 (see Table 1).

**TABLE 1: TABLE OF PHARMACOKINETIC PARAMETERS OF DROSPIRENONE AND ETHINYL ESTRADIOL TABLETS (Drospirenone 3 mg and Ethinyl Estradiol 0.02 mg)**

Cycle / Day	No. of Subjects	Drospirenone			
		C <sub>max</sub> <sup>1</sup> (ng/mL)	T <sub>max</sub> <sup>2</sup> (h)	AUC <sub>0-24h</sub> <sup>3</sup> (ng•h/mL)	t <sub>1/2</sub> <sup>4</sup> (h)
1/1	23	38.4 (25)	1.5 (1 to 2)	268 (19)	NA
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Cycle / Day	No. of Subjects	Ethinyl Estradiol			
		C <sub>max</sub> <sup>1</sup> (pg/mL)	T <sub>max</sub> <sup>2</sup> (h)	AUC <sub>0-24h</sub> <sup>3</sup> (pg•h/mL)	t <sub>1/2</sub> <sup>4</sup> (h)
1/1	23	32.8 (45)	1.5 (1 to 2)	108 (52)	NA
1/21	23	45.1 (35)	1.5 (1 to 2)	220 (57)	NA

**Effect of Food**  
The rate of absorption of DRSP and EE following single administration of a formulation similar to drospirenone and ethinyl estradiol tablets was slower under fed (high fat meal) conditions with the serum C<sub>max</sub> being reduced about 40% for both components. The extent of absorption of DRSP, however, remained unchanged. In contrast, the extent of absorption of EE was reduced by about 20% under fed conditions.

**Distribution**  
DRSP serum levels decline in two phases. The apparent volume of distribution of DRSP is approximately 4 L/kg and that of EE is reported to be approximately 4 to 5 L/kg.

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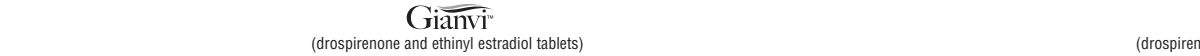
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DRSP serum levels are characterized by a terminal disposition phase half-life of approximately 30 hours after both single and multiple dose regimens. Excretion of DRSP was nearly complete after ten days and amounts excreted were slightly higher in feces compared to urine. DRSP was extensively metabolized and only trace amounts of unchanged DRSP were excreted in urine. In a study in 20 healthy women, the excretion of DRSP was 98.5% in feces and 1.5% in urine. The major metabolites excreted were glucuronide and sulfate conjugates. In feces, about 17 to 20% of the metabolites were excreted as glucuronides and sulfates.

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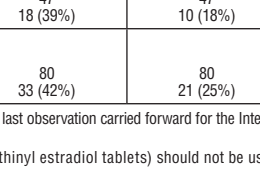
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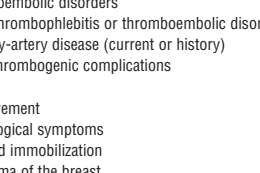
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		C <sub>max</sub> <sup>1</sup> (pg/mL)	T <sub>max</sub> <sup>2</sup> (h)	AUC <sub>0-24h</sub> <sup>3</sup> (pg•h/mL)	t <sub>1/2</sub> <sup>4</sup> (h)
1/1	23	32.8 (45)	1.5 (1 to 2)	108 (52)	NA
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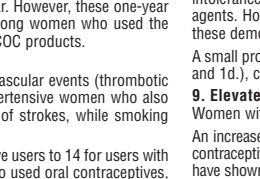
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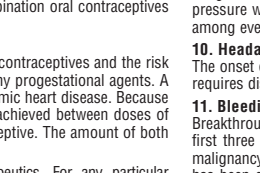
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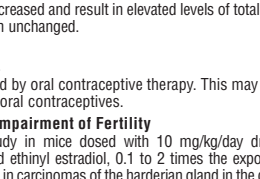
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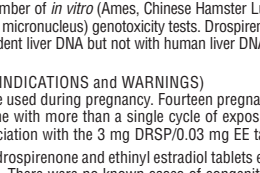
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**HOW SUPPLIED**  
Gianvi™ (drospirenone and ethinyl estradiol tablets) 3 mg/0.02 mg – 28-Day Regimen are available in packages of 3 blister packs (NDC 0095-5661-58).

Each blister card contains 24 active pink, round, unscored, film-coated tablets, debossed with stylized **b** on one side and **257** on the other side, each containing 3 mg of drospirenone and 0.02 mg of ethinyl estradiol, and 4 inert white, round, unscored tablets. Each blister card also contains 280 on one side and **280** on the other side. **KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.**

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

**REFERENCES**  
1. Dinger JG, Heinemann LAJ, et al: The safety of a drospirenone-containing oral contraceptive: final results from the European active surveillance study on oral contraceptives based on 14,275 women years of observation. *Contraception* 2007;75:344-354.  
2. Seeger JD, Loughlin J, Eng PM, et al: Risk of thromboembolism in women taking ethinyl estradiol/drospirenone and other oral contraceptives. *Obstetrics & Gynecology* 2007;110(3):587-593.  
3. van Hylckama Vlieg A, Heijerinkx FM, Vandendriessche JR, et al: The venous thrombotic risk of oral contraceptives, effects of estrogen dose and progestogen type: results of the MEGA case-control study. *BMJ* 2009;339:929-931.  
4. Lidegaard O, Lokkegaard E, Svendsen AL, et al: Hormonal contraception and risk of venous thromboembolism: national follow-up study. *BMJ* 2009; 339:b2890.

**BRIEF SUMMARY PATIENT PACKAGE INSERT**  
Gianvi™ (drospirenone and ethinyl estradiol tablets) containing the following:  
24 pink - "active" tablets  
4 white - "inert" tablets

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

**Gianvi™ (drospirenone and ethinyl estradiol tablets) is different from other birth control pills because it contains the progestin drospirenone. Drospirenone may increase potassium. Therefore, you should not take drospirenone and ethinyl estradiol tablets if you have kidney, liver or adrenal disease because this could cause serious heart and health problems.**

**• NSAIDs (ibuprofen [Motrin™, Advil™], naproxyn [Aleve™ and others] when taken long-term and daily for treatment of arthritis or other problems)**

**• Potassium-sparing diuretics (spironolactone and others)**

**• ACE inhibitors (Capoten™, Vasotec™, Zestril™ and others)**

**• Angiotensin-II receptor antagonists (Cozaar™, Diovan™, Avapro™ and others)**

**• Heparin**

**• Aldosterone antagonists**

Gianvi™ (drospirenone and ethinyl estradiol tablets) is an oral contraceptive, also known as a "birth control pill" or "the pill." Oral contraceptives are taken to prevent pregnancy, and when taken correctly without missing any pills, have a failure rate of approximately 1% per year (1 pregnancy per 100 women per year of use). The typical failure rate in pill users is approximately 5% per year (5 pregnancies per 100 women per year of use) when women who miss pills are included. Forgetting to take pills considerably increases the chances of pregnancy.

Gianvi™ (drospirenone and ethinyl estradiol tablets) may also be taken to treat moderate acne in women who are able to and wish to use the pill for birth control.

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

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

- have high blood pressure, diabetes, high cholesterol, or are obese
- have or have had clotting disorders, heart attack, stroke, angina pectoris (severe chest pains), cancer of the breast or sex organs, jaundice, or malignant or benign liver tumors.

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

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 adverse effects on the heart and blood vessels 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 not smoke.**

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

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

- Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), blockage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack and angina pectoris) or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and subsequent serious medical consequences. Women with migraine headaches also may be at increased risk of stroke when taking the pill.

- 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.

- High blood pressure, although blood pressure usually returns to normal when the pill is stopped.

- Cancer of the breast. Various studies give conflicting reports on the relationship between breast cancer and oral contraceptive use. Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly after using hormonal contraceptives at a younger age. After you stop using hormonal contraceptives, the chances of getting breast cancer begin to go back down. 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 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.

The symptoms associated with these serious side effects are discussed in the detailed leaflet given to you with your supply of pills. Notify your doctor or healthcare provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some antacids, as well as some herbal products such as St. John's Wort, may decrease oral contraceptive effectiveness.

Taking the pill may provide some important non-contraceptive benefits. These include less painful menstruation, less menstrual blood loss and anemia, fewer pelvic infections, and fewer cancers of the ovary and the lining of the uterus.

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

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**HOW TO TAKE THE PILL**

**IMPORTANT POINTS TO REMEMBER**  
**BEFORE YOU START TAKING YOUR PILLS:**  
1. BE SURE TO READ THESE DIRECTIONS:  
• Before you start taking your pills.  
• Anytime you are not sure what to do.

2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME. GIANVI™ TABLETS CAN BE TAKEN WITHOUT REGARD TO MEALS.

If you miss pills, you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant. See "WHAT TO DO IF YOU MISS PILLS" below.

3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1 TO 3 PACKS OF PILLS.

If you do have spotting or light bleeding or feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your healthcare provider.

4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills. On the days you take two pills, to make up for missed pills, you could also feel a little sick to your stomach.

5. IF YOU HAVE VOMITING (within 3 to 4 hours after you take your pill), you should follow the instructions for "WHAT TO DO IF YOU MISS PILLS" IF YOU HAD DIARRHEA, OR IF YOU TAKE CERTAIN MEDICINES, including some antibiotics and some herbal products such as St. John's Wort, your pills may not work as well.

Use a back-up method (such as condoms or spermicides) until you check with your healthcare provider.

6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your healthcare provider about how to make pill-taking easier or about using another method of birth control.

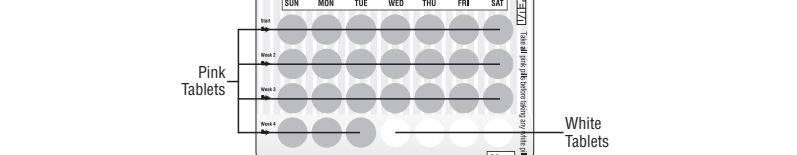
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3. ALSO FIND:  
1) Where on the pack to start taking pills.  
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4. BE SURE YOU HAVE READY AT ALL TIMES:  
• ANOTHER KIND OF BIRTH CONTROL (such as condoms or spermicides) to use as a back-up in case you miss pills.  
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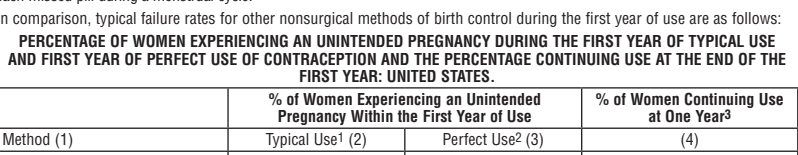
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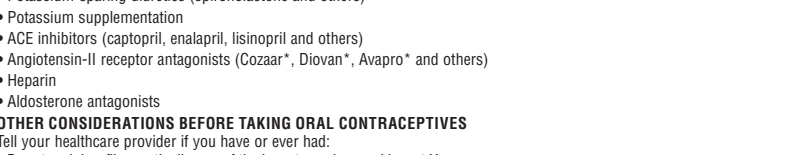
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Method of Control and Outcome	15 to 19 years		20 to 24 years		25 to 29 years		30 to 34 years		35 to 39 years		40 to 44 years	
	15 to 19 years	20 to 24 years	25 to 29 years	30 to 34 years	35 to 39 years	40 to 44 years	15 to 19 years	20 to 24 years	25 to 29 years	30 to 34 years	35 to 39 years	40 to 44 years
No fertility control methods <sup>1)</sup>	7.3	7.4	9.1	14.8	25.7	28.2						