JUNEL FE- junel fe tablet
Direct_Rx

Junel FE

Junel® 21 Day

(norethindrone acetate and ethinyl estradiol tablets USP)

Junel®1/20

(Each light yellow tablet contains 1 mg norethindrone acetate, USP and 20 mcg ethinyl estradiol, USP.)

Junel®1.5/30

(Each pink tablet contains 1.5 mg norethindrone acetate, USP and 30 mcg ethinyl estradiol, USP.)

Junel® Fe 28 Day

(norethindrone acetate and ethinyl estradiol tablets USP and ferrous fumarate tablets*)

*Ferrous fumarate tablets are not USP for dissolution and assay

Junel® Fe 1/20

(Each light yellow tablet contains 1 mg norethindrone acetate, USP and 20 mcg ethinyl estradiol, USP. Each brown tablet contains 75 mg ferrous fumarate, USP.)

Junel® Fe 1.5/30

(Each pink tablet contains 1.5 mg norethindrone acetate, USP and 30 mcg ethinyl estradiol, USP. Each brown tablet contains 75 mg ferrous fumarate, USP.)

Rx only

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

Junel® 21 and Junel® Fe 28 are progestogen-estrogen combinations.

Junel® Fe 1/20 and 1.5/30: Each provides a continuous dosage regimen consisting of 21 oral contraceptive tablets and seven ferrous fumarate tablets. The ferrous fumarate tablets are present to facilitate ease of drug administration via a 28-day regimen, are non-hormonal, and do not serve any therapeutic purpose.

Each light yellow tablet contains norethindrone acetate, USP (17α-ethinyl-19-nortestosterone acetate), 1 mg; ethinyl estradiol, USP (17α-ethinyl-1,3,5(10)-estratriene-3, 17β-diol), 20 mcg. Each light yellow tablet contains the following inactive ingredients: acacia, compressible sugar, D&C yellow no. 10 aluminum lake, lactose monohydrate, magnesium stearate and pregelatinized corn starch.

Each pink tablet contains norethindrone acetate, USP (17α-ethinyl-19-nortestosterone acetate), 1.5 mg; ethinyl estradiol, USP (17α-ethinyl-1,3,5(10)-estratriene-3, 17β-diol), 30 mcg. Each pink tablet contains the following inactive ingredients: acacia, compressible sugar, FD&C red no. 40 aluminum lake HT, lactose monohydrate, magnesium stearate and pregelatinized corn starch.

Each brown tablet contains the following ingredients: crospovidone, ferrous fumarate, hydrogenated vegetable oil, NF Type I and microcrystalline cellulose.

Norethindrone Acetate, USP

[Norethindrone Acetate, USP Structural Formula]

C22H28O3 M.W. 340.46

Ethinyl Estradiol, USP

[Ethinyl Estradiol, USP Structural Formula]

C20H24O2 M.W. 296.40

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

Pharmacokinetics

The pharmacokinetics of Junel have not been characterized; however, the following pharmacokinetic information regarding norethindrone acetate and ethinyl estradiol is taken from the literature.

Absorption

Norethindrone acetate appears to be completely and rapidly deacetylated to norethindrone after oral administration, since the disposition of norethindrone acetate is indistinguishable from that of orally administered norethindrone (1). Norethindrone acetate and ethinyl estradiol are subject to first-pass metabolism after oral dosing, resulting in an absolute bioavailability of approximately 64% for norethindrone and 43% for ethinyl estradiol (1-3).

Distribution

Volume of distribution of norethindrone and ethinyl estradiol ranges from 2 to 4 L/kg (1 to 3). Plasma protein binding of both steroids is extensive (greater than 95%); norethindrone binds to both albumin and sex hormone binding globulin, whereas ethinyl estradiol binds only to albumin (4).

Metabolism

Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites (5). A small amount of norethindrone acetate is metabolically converted to ethinyl estradiol. Ethinyl estradiol is also extensively metabolized, both by oxidation and by conjugation with sulfate and glucuronide. Sulfates are the major circulating conjugates of ethinyl estradiol and glucuronides predominate in urine.

The primary oxidative metabolite is 2-hydroxy ethinyl estradiol, formed by the CYP3A4 isoform of cytochrome P450. Part of the first-pass metabolism of ethinyl estradiol is believed to occur in gastrointestinal mucosa. Ethinyl estradiol may undergo enterohepatic circulation (6).

Excretion

Norethindrone and ethinyl estradiol are excreted in both urine and feces, primarily as metabolites (5, 6). Plasma clearance values for norethindrone and ethinyl estradiol are similar (approximately 0.4 L/hr/kg) (1-3).

Special Population

Race:

The effect of race on the disposition of Junel has not been evaluated.

Renal Insufficiency

The effect of renal disease on the disposition of Junel has not been evaluated. In premenopausal women with chronic renal failure undergoing peritoneal dialysis who received multiple doses of an oral contraceptive containing ethinyl estradiol and norethindrone, plasma ethinyl estradiol concentrations were higher and norethindrone concentrations were unchanged compared to concentrations in premenopausal women with normal renal function.

Hepatic Insufficiency

The effect of hepatic disease on the disposition of Junel has not been evaluated. However, ethinyl estradiol and norethindrone may be poorly metabolized in patients with impaired liver function.

Drug-Drug Interactions

Numerous drug-drug interactions have been reported for oral contraceptives. A summary of these is found under PRECAUTIONS, DRUG INTERACTIONS.

Junel21 and Junel Fe 28 are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

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

TABLE I: LOWEST EXPECTED AND TYPICAL FAILURE RATES DURING THE FIRST YEAR OF CONTINUOUS USE OF A METHOD

% Of Women Experiencing an Unintended Pregnancy in the First Year of Continuous Use

Method

Lowest Expected*

Typical**

(No contraception)

(85)

(85)

Oral contraceptives

combined
progestin only

0.1
0.5

3
N/A***
N/A***

Diaphragm with spermicidal cream or jelly

6

20

Spermicides alone (foam, creams, gels, vaginal suppositories, and vaginal film)

6

26

Vaginal Sponge
nulliparous
parous

9
20

20
40

Implant

0.05

0.05

Injection: depot medroxyprogesterone acetate

0.3

0.3

IUD
progesterone T
copper T 380A
LNg 20

1.5
0.6
0.1

2
0.8

0.1

Condom without spermicides
female
male

5
3

21
14

Cervical Cap with spermicidal cream or jelly
nulliparous
parous

9
26

20
40

Periodic abstinence (all methods)

1 to 9

25

Withdrawal

4

19

Female sterilization

0.5

0.5

Male sterilization

0.10

0.15

Adapted from RA Hatcher et al, Reference 7.

* The authors' best guess of the percentage of women expected to experience an accidental pregnancy among couples who initiate a method (not necessarily for the first time) and who use it consistently and correctly during the first year if they do not stop for any other reason.

** This term represents “typical” couples who initiate use of a method (not necessarily for the first time), who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

*** N/A-Data not available.

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
Cerebral vascular or coronary artery disease
Current diagnosis of, or history of, breast cancer, which may be hormone sensitive
Undiagnosed abnormal genital bleeding
Cholestatic jaundice of pregnancy or jaundice with prior pill use
Hepatic adenomas or carcinomas
Known or suspected pregnancy
Are receiving Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations (see WARNINGS, RISK OF LIVER ENZYME ELEVATIONS WITH CONCOMITANT HEPATITIS C TREATMENT).

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

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, 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 long-term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, 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 (adapted from REFERENCES 8 and 9 with the author's permission). For further information, the reader is referred to a text on epidemiological methods.

1. Thromboembolic Disorders and Other Vascular Problems

a. Myocardial infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity,

and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six (10-16). 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 infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases (17). Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and non-smokers over the age of 40 (Table II) among women who use oral contraceptives.

[Table II]

Adapted from P.M. Layde and V. Beral, Reference 18.

Adapted from P.M. Layde and V. Beral, Reference 18.

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity (19). In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism (20-24). Oral contraceptives have been shown to increase blood pressure among users (see section 9 in WARNINGS). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

b. Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to non-users to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease (9,10,25-30). 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 (31). The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped (8).

A two- to four-fold increase in relative risk of postoperative thromboembolic complications has been reported with the use of oral contraceptives (15,32). The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions (15,32). 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 to six weeks after delivery in women who elect not to breastfeed.

c. Cerebrovascular disease

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 (greater than 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 (33-35).

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 (36). The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users, and 25.7 for users with severe hypertension (36). The attributable risk is also greater in older women (9).

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 (37-39). A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents (20-22). 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 progestin and the nature of the progestin used in the contraceptives. The amount and activity 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 oral contraceptive, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing the lowest dose of estrogen which produces satisfactory results for the patient.

e. Persistence of risk of vascular disease

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40 to 49 years who had used oral contraceptives for 5 or more years, but this increased risk was not demonstrated in other age groups (14). In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small (40). However, both studies were performed with oral contraceptive formulations containing 50 mcg or higher of estrogens.

2. Estimates of Mortality from Contraceptive Use

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (Table III). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. The observation of a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970's but not reported until 1983 (41). However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral contraceptive use to women who do not have the various risk factors listed in this labeling.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed (Porter JB, Hunter J, Jick H, et al. Oral contraceptives and nonfatal vascular disease. Obstet Gynecol 1985;66:1-4; and Porter JB, Hershel J, Walker AM. Mortality among oral contraceptive users.

Obstet Gynecol 1987;70:29-32), the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception.

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

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

Method of control and outcome

15 to 19

20 to 24

25 to 29

30 to 34

35 to 39

40 to 44

No fertility control methods

7.0

7.4

9.1

14.8

25.7

28.2

Oral contraceptives 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.

Adapted from H.W. Ory, Reference 41.

3. Malignant Neoplasms

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

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

Cervical Cancer
Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women (51-54).(However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

4. Hepatic Neoplasia

Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use (55). Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage (56,57).

Studies from Britain have shown an increased risk of developing hepatocellular carcinoma (58-60) in long-term (greater than 8 years) oral contraceptive users. However, these cancers are extremely rare in the U.S., and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users.

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

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

6. Ocular Lesions

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

7. Oral Contraceptive Use Before and During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy (61-63). Studies also do not suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb reduction defects are concerned (61,62,64,65), when taken inadvertently during early pregnancy.

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

It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued if pregnancy is confirmed.

8. Gallbladder Disease

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens (66,67). More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal (68-70). The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

9. Carbohydrate And Lipid Metabolic Effects

Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users (23). Oral contraceptives containing greater than 75 mcg of estrogens cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance (71). Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents (23,72). However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose (73). 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.

10. Elevated Blood Pressure

An increase in blood pressure has been reported in women taking oral contraceptives (74) and this increase is more likely in older oral contraceptive users (75) and with continued use (74). Data from the Royal College of General Practitioners (18) 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 (76) should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely, and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives (75), and there is no difference in the occurrence of hypertension among ever and never users (74,76,77).

11. Headache

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

12. Bleeding Irregularities

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

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was preexistent.

1. 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

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

3. Lipid Disorders

Women who are being treated for hyperlipidemia 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.

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.

7. Contact Lenses

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

8. Drug Interactions

Effects of Other Drugs on Oral Contraceptives (78)

Rifampin: Metabolism of both norethindrone and ethinyl estradiol is increased by rifampin. A reduction in contraceptive effectiveness and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin.

Anticonvulsants: Anticonvulsants such as phenobarbital, phenytoin, and carbamazepine, have been shown to increase the metabolism of ethinyl estradiol and/or norethindrone, which could result in a reduction in contraceptive effectiveness.

Troglitazone: Administration of troglitazone with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both by approximately 30%, which could result in a reduction in contraceptive effectiveness.

Antibiotics: Pregnancy while taking oral contraceptives has been reported when the oral contraceptives were administered with antimicrobials such as ampicillin, tetracycline, and griseofulvin. However, clinical pharmacokinetic studies have not demonstrated any consistent effect of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.

Atorvastatin: Coadministratrion of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively.

Concomitant Use with HCV Combination Therapy– Liver Enzyme Elevation Do not co-administer Junel with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations (see Warnings, RISK OF LIVER ENZYME ELEVATIONS WITH CONCOMITANT HEPATITIS C TREATMENT).

Other: Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol concentrations, possibly by inhibition of conjugation. A reduction in contraceptive effectiveness and increased incidence of breakthrough bleeding has been suggested with phenylbutazone.

Effects of Oral Contraceptives on Other Drugs

Oral contraceptive combinations containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of oral contraceptives. In addition, oral contraceptives may induce the conjugation of other

compounds. Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine, and clofibric acid have been noted when these drugs were administered with oral contraceptives.

9. Interactions With Laboratory Tests

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

Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
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.
Other binding proteins may be elevated in serum.
Sex-binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged.
Triglycerides may be increased.
Glucose tolerance may be decreased.
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

See CONTRAINDICATIONS and WARNINGS sections.

12. Nursing Mothers

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

13. Pediatric Use

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

See patient labeling printed below.

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

Post Marketing Experience

Five studies that compared breast cancer risk between ever-users (current or past use) of COCs and never-users of COCs reported no association between ever use of COCs and breast cancer risk, with effect estimates ranging from 0.90 - 1.12 (Figure 1).

Three studies compared breast cancer risk between current or recent COC users (<6 months since last use) and never users of COCs (Figure 1). One of these studies reported no association between breast cancer risk and COC use. The other two studies found an increased relative risk of 1.19 - 1.33 with current or recent use. Both of these studies found an increased risk of breast cancer with current use of longer duration, with relative risks ranging from 1.03 with less than one year of COC use to approximately 1.4 with more than 8-10 years of COC use.

FIGURE 1: RELEVANT STUDIES OF RISK OF BREAST CANCER WITH COMBINED ORAL CONTRACEPTIVES

[image 1]

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

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

Mesenteric thrombosis
Retinal thrombosis

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

Nausea
Vomiting
Gastrointestinal symptoms (such as abdominal cramps and bloating)
Breakthrough bleeding
Spotting
Change in menstrual flow
Amenorrhea
Temporary infertility after discontinuation of treatment
Edema
Melasma which may persist
Breast changes: tenderness, enlargement, secretion
Change in weight (increase or decrease)
Change in cervical erosion and secretion
Diminution in lactation when given immediately postpartum
Cholestatic jaundice
Migraine
Rash (allergic)
Mental depression

Reduced tolerance to carbohydrates
Vaginal candidiasis
Change in corneal curvature (steepening)
Intolerance to contact lenses

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

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

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.

The tablet dispenser has been designed to make oral contraceptive dosing as easy and as convenient as possible. The tablets are arranged in either three or four rows of seven tablets each, with the days of the week appearing on the tablet dispenser above the first row of tablets.

Note: Each tablet dispenser has been preprinted with the days of the week, starting with Sunday, to facilitate a Sunday-Start regimen. Six different days of the week stickers have been provided with the Detailed Patient & Brief Summary Patient Package Insert in order to accommodate a Day-1 Start regimen. If the patient is using the Day-1 Start regimen, she should place the self-adhesive days of the week sticker that corresponds to her starting day over the preprinted days.

Important: The patient should be instructed to use an additional method of protection until after the first week of administration in the initial cycle when utilizing the Sunday-Start regimen.

The possibility of ovulation and conception prior to initiation of use should be considered.

Dosage and Administration for 21-Day Dosage Regimen

To achieve maximum contraceptive effectiveness, Junel 21 must be taken exactly as

directed and at intervals not exceeding 24 hours. Junel 21 provides the patient with a convenient tablet schedule of “3 weeks on --1 week off”. Two dosage regimens are described, one of which may be more convenient or suitable than the other for an individual patient. For the initial cycle of therapy, the patient begins her tablets according to the Day-1 Start or Sunday-Start regimen. With either regimen, the patient takes one tablet daily for 21 consecutive days followed by one week of no tablets.

Sunday-Start Regimen:The patient begins taking tablets from the top row on the first Sunday after menstrual flow begins. When menstrual flow begins on Sunday, the first tablet is taken on the same day. The last tablet in the dispenser will then be taken on a Saturday, followed by no tablets for a week (7 days). For all subsequent cycles, the patient then begins a new 21-tablet regimen on the eighth day, Sunday, after taking her last tablet. Following this regimen, of 21 days on--7 days off, the patient will start all subsequent cycles on a Sunday.
Day-1 Regimen:The first day of menstrual flow is Day 1. The patient places the self-adhesive days of the week sticker that corresponds to her starting day over the preprinted days on the blister card. She starts taking one tablet daily, beginning with the first tablet in the top row. The patient completes her 21-tablet regimen when she has taken the last tablet in the tablet dispenser. She will then take no tablets for a week (7 days). For all subsequent cycles, the patient begins a new 21-tablet regimen on the eighth day after taking her last tablet, again starting with the first tablet in the top row after placing the appropriate days of the week sticker over the preprinted days on the blister card. Following this regimen of 21 days on--7 days off, the patient will start all subsequent cycles on the same day of the week as the first course. Likewise, the interval of no tablets will always start on the same day of the week.

Tablets should be taken regularly with a meal or at bedtime. It should be stressed that efficacy of medication depends on strict adherence to the dosage schedule.

Special Notes on Administration

Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after discontinuing medication. If spotting occurs while on the usual regimen of one tablet daily, the patient should continue medication without interruption.

If the patient forgets to take one or more tablets, the following is suggested:

One tablet is missed

take tablet as soon as remembered
take next tablet at the regular time

Two consecutive tablets are missed (week 1 or week 2)

take two tablets as soon as remembered
take two tablets the next day
use another birth control method for seven days following the missed tablets

Two consecutive tablets are missed (week 3)

Sunday-Start Regimen:

take one tablet daily until Sunday
discard remaining tablets
start new pack of tablets immediately (Sunday)
use another birth control method for seven days following the missed tablets

Day-1 Start Regimen:

discard remaining tablets
start new pack of tablets that same day
use another birth control method for seven days following the missed tablets

Three(or more) consecutive tablets are missed

Sunday-Start Regimen:

take one tablet daily until Sunday
discard remaining tablets
start new pack of tablets immediately (Sunday)
use another birth control method for seven days following the missed tablets

Day-1 Start Regimen:

discard remaining tablets
start new pack of tablets that same day
use another birth control method for seven days following the missed tablets

The possibility of ovulation occurring increases with each successive day that scheduled tablets are missed. While there is little likelihood of ovulation occurring if only one tablet is missed, the possibility of spotting or bleeding is increased. This is particularly likely to occur if two or more consecutive tablets are missed.

In the rare case of bleeding which resembles menstruation, the patient should be advised to discontinue medication and then begin taking tablets from a new tablet dispenser on the next Sunday or the first day (Day 1), depending on her regimen. Persistent bleeding which is not controlled by this method indicates the need for reexamination of the patient, at which time nonfunctional causes should be considered.

Dosage and Administration for 28-Day Dosage Regimen

To achieve maximum contraceptive effectiveness, Junel Fe should be taken exactly as directed and at intervals not exceeding 24 hours.

Junel Fe provides a continuous administration regimen consisting of 21 light yellow or pink tablets of Junel and 7 brown non-hormone containing tablets of ferrous fumarate. The ferrous fumarate tablets are present to facilitate ease of drug administration via a 28-day regimen and do not serve any therapeutic purpose. There is no need for the patient to count days between cycles because there are no “off-tablet days.”

Sunday-Start Regimen: The patient begins taking the first light yellow or pink tablet from the top row of the dispenser (labeled Sunday) on the first Sunday after menstrual flow begins. When the menstrual flow begins on Sunday, the first light yellow or pink tablet is taken on the same day. The patient takes one light yellow or pink tablet daily for 21 days. The last light yellow or pink tablet in the dispenser will be taken on a Saturday. Upon completion of all 21 light yellow or pink tablets, and without interruption, the patient takes one brown tablet daily for 7 days. Upon completion of this first course of tablets, the patient begins a second course of 28-day tablets, without interruption, the next day (Sunday), starting with the Sunday light yellow or pink tablet in the top row. Adhering to this regimen of one light yellow or pink tablet daily for 21 days, followed without interruption by one brown tablet daily for seven days, the patient will start all subsequent cycles on a Sunday.

Day-1 Regimen: The first day of menstrual flow is Day 1. The patient places the self-adhesive days of the week sticker that corresponds to her starting day over the preprinted days on the blister card. She starts taking one light yellow or pink tablet daily, beginning with the first light yellow or pink tablet in the top row. After the last light yellow or pink tablet (at the end of the third row) has been taken, the patient will then take the brown tablets for a week (7 days). For all subsequent cycles, the patient begins a new 28 tablet regimen on the eighth day after taking her last light yellow or pink tablet, again starting with the first tablet in the top row after placing the appropriate days of the week sticker over the preprinted days on the blister card. Following this regimen of 21 light yellow or pink tablets and 7 brown tablets, the patient will start all subsequent cycles on the same day of the week as the first course.

Tablets should be taken regularly with a meal or at bedtime. It should be stressed that efficacy of medication depends on strict adherence to the dosage schedule.

Special Notes on Administration

Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after the brown tablets have been started. In any event, the next course of tablets should be started without interruption. If spotting occurs while the patient is taking light yellow or pink tablets, continue medication without interruption.

If the patient forgets to take one or more light yellow or pink tablets, the following is suggested:

One tablet is missed

take tablet as soon as remembered
take next tablet at the regular time

Two consecutive tablets are missed (week 1 or week 2)

take two tablets as soon as remembered
take two tablets the next day
use another birth control method for seven days following the missed tablets

Two consecutive tablets are missed (week 3)

Sunday-Start Regimen:

take one tablet daily until Sunday
discard remaining tablets
start new pack of tablets immediately (Sunday)
use another birth control method for seven days following the missed tablets

Day-1 Start Regimen:

discard remaining tablets
start new pack of tablets that same day
use another birth control method for seven days following the missed tablets

Three(or more) consecutive tablets are missed

Sunday-Start Regimen:

take one tablet daily until Sunday
discard remaining tablets
start new pack of tablets immediately (Sunday)

use another birth control method for seven days following the missed tablets

Day-1 Start Regimen:

discard remaining tablets
start new pack of tablets that same day
use another birth control method for seven days following the missed tablets

The possibility of ovulation occurring increases with each successive day that scheduled light yellow or pink tablets are missed. While there is little likelihood of ovulation occurring if only one light yellow or pink tablet is missed, the possibility of spotting or bleeding is increased. This is particularly likely to occur if two or more consecutive light yellow or pink tablets are missed.

If the patient forgets to take any of the seven brown tablets in week four, those brown tablets that were missed are discarded and one brown tablet is taken each day until the pack is empty. A back-up birth control method is not required during this time. A new pack of tablets should be started no later than the eighth day after the last light yellow or pink tablet was taken.

In the rare case of bleeding which resembles menstruation, the patient should be advised to discontinue medication and then begin taking tablets from a new tablet dispenser on the next Sunday or the first day (Day-1), depending on her regimen. Persistent bleeding which is not controlled by this method indicates the need for reexamination of the patient, at which time nonfunctional causes should be considered.

Use of Oral Contraceptives in the Event of a Missed Menstrual Period

If the patient has not adhered to the prescribed dosage regimen, the possibility of pregnancy should be considered after the first missed period and oral contraceptives should be withheld until pregnancy has been ruled out.
If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.

After several months on treatment, bleeding may be reduced to a point of virtual absence. This reduced flow may occur as a result of medication, in which event it is not indicative of pregnancy.

Junel® 1/20 (21 Tablets) (norethindrone acetate 1 mg and ethinyl estradiol 20 mcg tablets, USP) are packaged in cartons of three blister cards. Each card contains 21 light yellow, round, flat-faced, beveled-edge, unscored tablets debossed with stylized b on one side and 977 on the other side. (NDC 0555-9025-42).

Junel® Fe 1/20 (28 Tablets) (norethindrone acetate 1 mg and ethinyl estradiol 20 mcg tablets, USP, and ferrous fumarate tablets) are packaged in cartons of six blister cards. Each card contains 21 light yellow, round, flat-faced, beveled-edge, unscored tablets debossed with stylized b on one side and 977 on the other side and 7 brown, round, flat-faced, beveled-edge, unscored tablets debossed with stylized b on one side and 247 on the other side. Each brown tablet contains 75 mg ferrous fumarate. The ferrous fumarate tablets are present to facilitate ease of drug administration via a 28-day regimen, are non-hormonal, and do not serve any therapeutic purpose. (NDC 0555-9026-58).

Junel® 1.5/30 (21 Tablets) (norethindrone acetate 1.5 mg and ethinyl estradiol 30 mcg tablets, USP) are packaged in cartons of three blister cards. Each card contains 21 pink,

round, flat-faced, beveled-edge, unscored tablets debossed with stylized b on one side and 978 on the other side. (NDC 0555-9027-42).

Junel® Fe 1.5/30 (28 Tablets) (norethindrone acetate 1.5 mg and ethinyl estradiol 30 mcg tablets, USP, and ferrous fumarate tablets) are packaged in cartons of six blister cards. Each card contains 21 pink, round, flat-faced, beveled-edge, unscored tablets debossed with stylized b on one side and 978 on the other side and 7 brown, round, flat-faced, beveled-edge, unscored tablets debossed with stylized b on one side and 247 on the other side. Each brown tablet contains 75 mg ferrous fumarate. The ferrous fumarate tablets are present to facilitate ease of drug administration via a 28-day regimen, are non-hormonal, and do not serve any therapeutic purpose. (NDC 0555-9028-58).

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

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Teva Pharmaceuticals USA, Inc.
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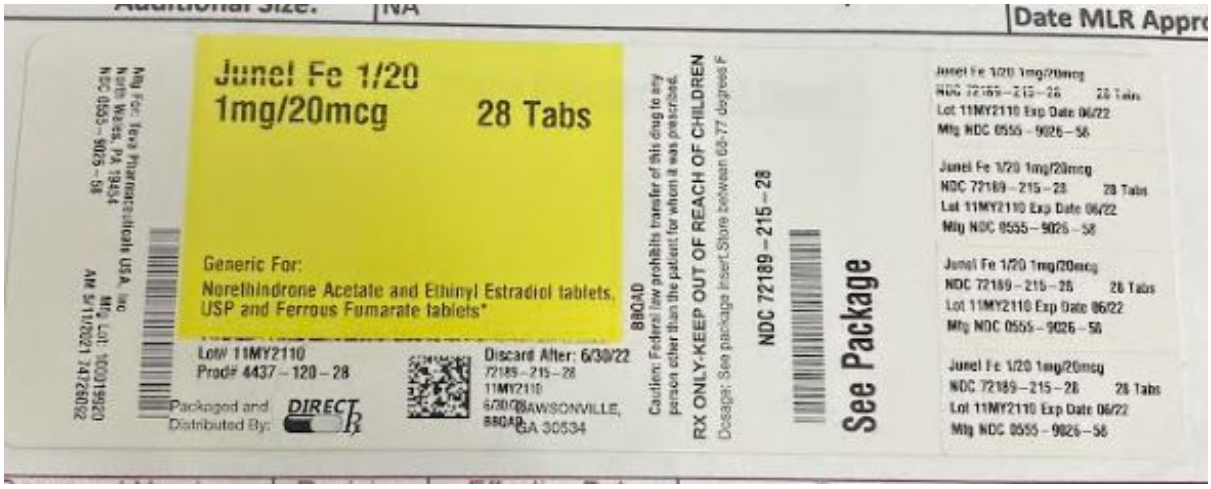
Rev. C 7/2022



JUNEL FE

junel fe tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:72189-215(NDC:0555-9025)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ETHINYL ESTRADIOL (UNII: 423D2T571U) (ETHINYL ESTRADIOL - UNII:423D2T571U)	ETHINYL ESTRADIOL	20 ug
NORETHINDRONE ACETATE (UNII: 9S44LIC7OJ) (NORETHINDRONE - UNII:T18F433X4S)	NORETHINDRONE ACETATE	1 mg

Inactive Ingredients	
Ingredient Name	**Strength**
MALTODEXTRIN (UNII: 7CVR7L4A2D)	
SUCROSE (UNII: C151H8M554)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
STARCH, CORN (UNII: O8232NY3SJ)	
ACACIA (UNII: 5C5403N26O)	
D&C YELLOW NO. 10 ALUMINUM LAKE (UNII: CQ3XH3DET6)	

Product Characteristics			
Color	yellow (light-yellow)	**Score**	no score
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	b;977
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72189-215-28	28 in 1 POUCH; Type 0: Not a Combination Product	10/06/2021	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076380	10/06/2021	

Labeler - Direct_Rx (079254320)

Registrant - Direct_Rx (079254320)

Establishment

Name	Address	ID/FEI	Business Operations
Direct_Rx		079254320	relabel(72189-215)

Revised: 1/2025 Direct_Rx