

## PHYSICIAN LABELING

### Norminest® Fe Tablets

(norethindrone and ethinyl estradiol)

### Norquest® Fe Tablets

(norethindrone and ethinyl estradiol)

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

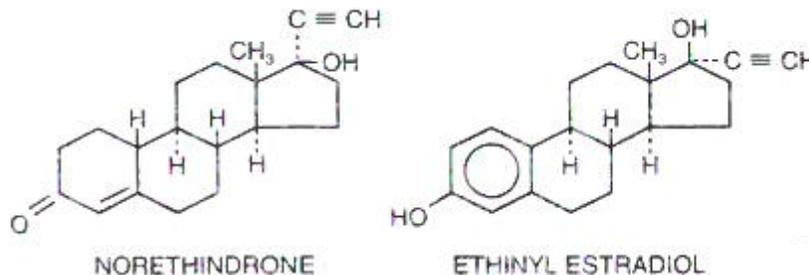
## ORAL CONTRACEPTIVE AGENTS

### DESCRIPTION

**Norminest® Fe Tablets** provide a continuous oral contraceptive regimen consisting of 21 blue tablets containing norethindrone 0.5 mg and ethinyl estradiol 0.035 mg and 7 brown tablets containing ferrous fumarate 75 mg.

**Norquest® Fe Tablets** provide a continuous oral contraceptive regimen consisting of 21 yellow-green tablets containing norethindrone 1 mg and ethinyl estradiol 0.035 mg and 7 brown tablets containing ferrous fumarate 75 mg.

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



### INACTIVE INGREDIENTS

The blue Norminest tablets contain the following inactive ingredients: FD&C Blue No.1, lactose, magnesium stearate, povidone and starch.

The yellow-green Norquest tablets contain the following inactive ingredients: D&C Green No. 5, D&C Yellow No. 10, lactose, magnesium stearate, povidone and starch.

The inactive brown tablets in the 28-day regimen contain the following ingredients: ferrous fumarate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate and starch.

The iron tablets are not included for any therapeutic purpose but to provide a daily tablet regimen for days 22 through 28 of the cycle.

### **CLINICAL PHARMACOLOGY**

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

### **INDICATIONS AND USAGE**

Oral contraceptives are indicated for the prevention of pregnancy in women who elect to use these products 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.<sup>1</sup> 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 Accidental Pregnancy in the First Year of Continuous use

Method	Lowest Expected <sup>a</sup>	Typical <sup>b</sup>
(No Contraception)	(85)	(85)
Oral contraceptives		3
combined	0.1	N/A <sup>c</sup>
progestogen only	0.5	N/A <sup>c</sup>
Diaphragm with spermicidal cream or jelly	6	18
Spermicides alone (foam, creams, jellies and vaginal suppositories)	3	21
Vaginal Sponge		
Nulliparous	6	18
Multiparous	>9	>28
IUD (medicated)	2	3 <sup>d</sup>
Condom without spermicides	2	12
Periodic abstinence (all methods)	1-9	20
Injectable progestogen <sup>e</sup>	0.4	0.4
Implants	0.04	0.04
Female sterilization	0.2	0.4
Male sterilization	0.1	0.15

Adapted from J. Trussell, Table 1<sup>1</sup>

<sup>a</sup> 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.

<sup>b</sup> 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. The authors derive these data largely from the National Surveys of Family Growth (NSFG), 1976 and 1982.

<sup>c</sup> N/A-Data not available from the NSFG, 1976 and 1982.

<sup>d</sup> Combined typical rate for both medicated and non-medicated IUD. The rate for medicated IUD alone is not available.

<sup>e</sup> All forms.

## CONTRAINDICATIONS

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

- Thrombophlebitis or thromboembolic disorders
- A past history of deep vein thrombophlebitis or thromboembolic disorders
- Cerebral vascular or coronary artery disease

- Known or suspected carcinoma of the breast
- Carcinoma of the endometrium, and known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior pill use
- Hepatic adenomas, carcinomas or benign liver tumors
- Known or suspected pregnancy

Women who are receiving Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for alanine aminotransferase (ALT) elevations (see **WARNINGS, RISK OF LIVER ENZYME ELEVATIONS WITH CONCOMITANT HEPATITIS C TREATMENT**).

#### **WARNINGS**

**Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with 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 and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, hypercholesterolemia, obesity and diabetes.<sup>2-5</sup>

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 formulations containing 0.05 mg or higher of estrogen.<sup>6-11</sup> The effects of long-term use with lower dose formulations of both estrogens and progestogens remain to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease. Relative risk, the ratio of the incidence of a disease among oral contraceptive users to that among non-users, cannot be assessed directly from case control studies, but the odds ratio obtained is a measure of relative risk. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide not only a measure of the relative risk but a measure of attributable risk, which is the *difference* in the incidence of disease between oral contraceptive users and non-users. The attributable risk does provide information about the actual occurrence of a disease in the population.<sup>12-13</sup>

### **1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS**

#### **a. Myocardial Infarction**

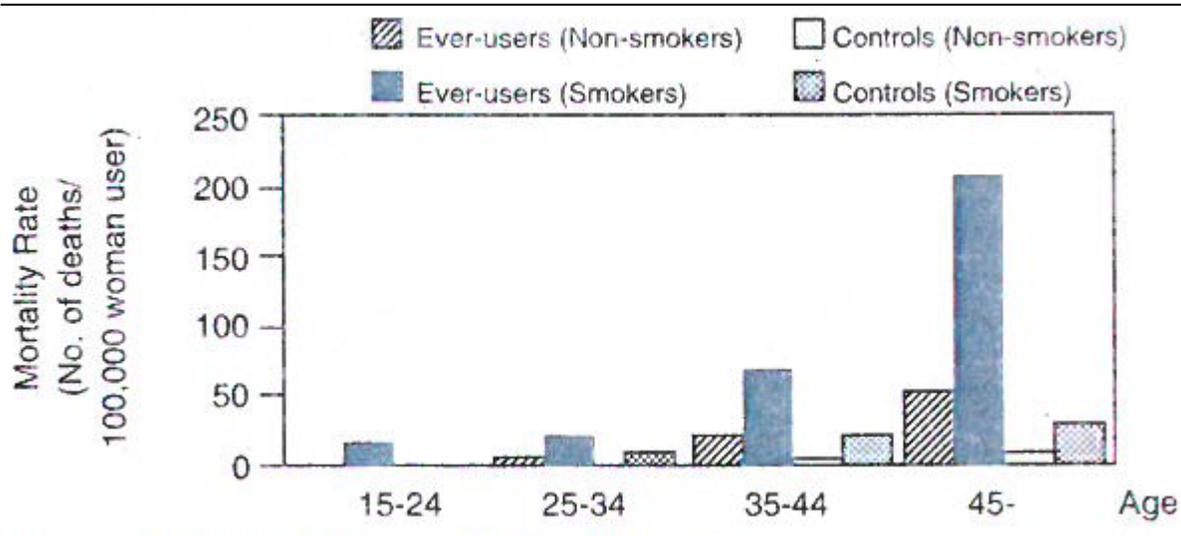
An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as

hypertension, hypercholesterolemia, morbid obesity and diabetes.<sup>2-5, 13</sup> The relative risk of heart attack for current oral contraceptive users has been estimated to be 2 to 6.<sup>2, 14-19</sup> The risk is very low under the age of 30. However, there is the possibility of a risk of cardiovascular disease even in very young women who take oral contraceptives.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women 35 or older, with smoking accounting for the majority of excess cases.<sup>20</sup>

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

TABLE II: CIRCULATORY DISEASE MORTALITY RATES PER 100,000 WOMAN YEARS BY AGE, SMOKING STATUS AND ORAL CONTRACEPTIVE USE



Adapted from P.M. Layde and V. Beral, Table V<sup>16</sup>

Oral contraceptives may compound the effects of well-known risk factors for coronary artery disease, such as hypertension, diabetes, hyperlipidemias, hypercholesterolemia, age and obesity.<sup>3, 13, 21</sup> In particular, some progestogens are known to decrease HDL cholesterol and impair oral glucose tolerance, while estrogens may create a state of hyperinsulinism.<sup>21-25</sup> Oral contraceptives have been shown to increase blood pressure among users (see **WARNINGS**, section 10). 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.<sup>12, 13, 26-31</sup> One cohort study has shown the relative risk to be somewhat lower, about 3 for new cases (subjects with no past history of venous thrombosis or varicose veins) and about

4.5 for new cases requiring hospitalization.<sup>32</sup> The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped.<sup>12</sup>

A 2- to 6-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives.<sup>18</sup> If feasible, oral contraceptives should be discontinued at least 4 weeks prior to and for 2 weeks after elective surgery and during and following prolonged immobilization. Since the immediate postpartum period also is associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than 4 to 6 weeks after delivery in women who elect not to breast feed.<sup>33</sup>

### **c. Cerebrovascular diseases**

An increase in both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes) has been shown in users of oral contraceptives. In general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and non-users for both types of strokes while smoking interacted to increase the risk for hemorrhagic strokes.<sup>34</sup>

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.<sup>35</sup> 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.<sup>35</sup> The attributable risk also is greater in women 35 or older and among smokers.<sup>13</sup>

### **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.<sup>36-38</sup> A decline in serum high density lipoproteins (HDL) has been reported with some progestational agents.<sup>22-24</sup> A decline in serum high density lipoproteins has been associated with an increased incidence of ischemic heart disease.<sup>39</sup> Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogens used in the contraceptives. The amount of both hormones should be considered in the choice of an oral contraceptive.<sup>37</sup>

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

### **e. Persistence of risk of vascular disease**

There are three studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives.<sup>17, 34, 40</sup> 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 40-49 years who had used oral contraceptives for 5 or more years, but this increased risk was not demonstrated in other age groups.<sup>17</sup> 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.<sup>40</sup> Subarachnoid

hemorrhage also has a significantly increased relative risk after termination of use of oral contraceptives.<sup>34</sup> However, these studies were performed with oral contraceptive formulations containing 0.05 mg or higher of estrogen.

## **2. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE**

One study gathered data from a variety of sources which have estimated the mortality rates associated with different methods of contraception at different ages (see Table III).<sup>41</sup> 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 in the U.S. until 1983.<sup>16, 41</sup> 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<sup>78, 79</sup>, 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.<sup>80</sup>

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

Method of control and outcome	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

\*Deaths are birth-related

\*\*Deaths are method-related

Estimates adapted from H. W. Ory, Table 3<sup>41</sup>

### 3. CARCINOMA OF THE BREAST AND REPRODUCTIVE ORGANS

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical cancer in women using oral contraceptives. The evidence in the literature suggests that use of oral contraceptives is not associated with an increase in the risk of developing breast cancer, regardless of the age and parity of first use or with most of the marketed brands and doses.<sup>42, 43</sup> The Cancer and Steroid Hormone study also showed no latent effect on the risk of breast cancer for at least a decade following long-term use.<sup>43</sup> A few studies have shown a slightly increased relative risk of developing breast cancer,<sup>44-47</sup> although the methodology of these studies, which included differences in examination of users and non-users and differences in age at start of use, has been questioned.<sup>47-49</sup> Some studies have reported an increased relative risk of developing breast cancer, particularly at a younger age. This increased relative risk appears to be related to duration of use.<sup>81, 82</sup>

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.<sup>50-53</sup> However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

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

### 4. HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral contraceptive use although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases per 100,000 for users, a risk that increases after 4 or more years of use.<sup>54</sup> Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.<sup>55-56</sup>

Studies in the United States and Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users.<sup>57-59</sup> However, these cancers are extremely

rare in the United States and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users is less than 1 per 1,000,000 users.

#### **5. RISK OF LIVER ENZYME ELEVATIONS WITH CONCOMITANT HEPATITIS C TREATMENT**

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

#### **6. OCULAR LESIONS**

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

#### **7. ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY**

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy.<sup>60-62</sup> More recent studies do not suggest a teratogenic effect, particularly insofar as cardiac anomalies 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.<sup>65-66</sup> More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal.<sup>67</sup> The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.<sup>68</sup>

#### **9. CARBOHYDRATE AND LIPID METABOLIC EFFECTS**

Oral contraceptives have been shown to impair oral glucose tolerance.<sup>69</sup> Oral contraceptives containing greater than 0.075 mg of estrogen cause glucose intolerance with impaired insulin secretion, while lower doses of estrogen may produce less glucose intolerance.<sup>70</sup> Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents.<sup>25,71</sup> However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose.<sup>69</sup> Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

Some women may develop persistent hypertriglyceridemia while on the pill.<sup>72</sup> As discussed earlier (see **WARNINGS**, sections 1a and 1d.), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.<sup>23</sup>

#### **10. ELEVATED BLOOD PRESSURE**

An increase in blood pressure has been reported in women taking oral contraceptives. The incidence of risk also was reported to increase with continued use and among older women.<sup>66</sup> Data from the Royal

College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestogens.

Women with a history of hypertension or hypertension-related diseases or renal disease should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives and there is no difference in the occurrence of hypertension among ever- and never-users.<sup>73-75</sup>

### **11. HEADACHE**

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

### **12. BLEEDING IRREGULARITIES**

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first 3 months of use. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

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

## **PRECAUTIONS**

### **GENERAL**

**PATIENTS SHOULD BE COUNSELED THAT THIS PRODUCT DOES NOT PROTECT AGAINST HIV (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.**

#### **1. PHYSICAL EXAMINATION AND FOLLOW-UP**

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

#### **2. LIPID DISORDERS**

Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult.

#### **3. LIVER FUNCTION**

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

#### **4. FLUID RETENTION**

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

#### **5. EMOTIONAL DISORDERS**

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

#### **6. CONTACT LENSES**

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

#### **7. DRUG INTERACTIONS**

Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation

Do not co-administer Norminest/Norquest 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**).

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

#### **8. INTERACTIONS WITH LABORATORY TESTS**

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

- a. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
- b. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 concentration is unaltered.
- c. Other binding proteins may be elevated in serum.
- d. Sex steroid binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged.
- e. Triglycerides may be increased.
- f. Glucose tolerance may be decreased.
- g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

#### **9. CARCINOGENESIS**

See **WARNINGS** section.

#### **10. PREGNANCY**

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

#### **11. NURSING MOTHERS**

Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing

the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

### **INFORMATION FOR THE 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, carcinomas or benign liver tumors

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

- Mesenteric thrombosis
- Retinal thrombosis

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

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

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

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

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

#### **OVERDOSAGE**

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

#### **NON-CONTRACEPTIVE HEALTH BENEFITS**

The following non-contraceptive health benefits related to the use of oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing estrogen doses exceeding 0.035 mg of ethinyl estradiol.<sup>6-11</sup>

Effects on menses:

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

Effects related to inhibition of ovulation:

- Decreased incidence of functional ovarian cysts
- Decreased incidence of ectopic pregnancies

Effects from long-term use:

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

### DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, oral contraceptives must be taken exactly as described and at intervals not exceeding 24 hours.

**28-Day Schedule:** For a SUNDAY START when menstrual flow begins on or before Sunday, the first tablet (blue or yellow-green) is taken on that day.

For a Day 5 start, count the first day of menstrual flow as Day 1 and the first tablet (blue or yellow-green) is then taken on Day 5. With either a SUNDAY START or DAY 5 START, 1 tablet (blue or yellow-green) is taken each day at the same time for 21 days. Then the brown tablets are taken for 7 days, whether bleeding has stopped or not. After all 28 tablets have been taken, whether bleeding has stopped or not, the same dosage schedule is repeated beginning on the following day.

### INSTRUCTIONS TO PATIENTS

- To achieve maximum contraceptive effectiveness, the oral contraceptive pill must be taken exactly as directed and at intervals not exceeding 24 hours.
- Important: Women should be instructed to use an additional method of protection until after the first 7 days of administration *in the initial cycle*.
- Due to the normally increased risk of thromboembolism occurring postpartum, women should be instructed not to initiate treatment with oral contraceptives earlier than 4 weeks after a full-term delivery. If pregnancy is terminated in the first 12 weeks, the patient should be instructed to start oral contraceptives immediately or within 7 days. If pregnancy is terminated after 12 weeks, the patient should be instructed to start oral contraceptives after 2 weeks.<sup>33, 77</sup>
- If spotting or breakthrough bleeding should occur, the patient should continue the medication according to the schedule. Should spotting or breakthrough bleeding persist, the patient should notify her physician.
- If the patient misses 1 pill, she should be instructed to take it as soon as she remembers and then take the next pill at the regular time. The patient should be advised that missing a pill can cause spotting or light bleeding and that she may be a little sick to her stomach on the days she takes the missed pill with her regularly scheduled pill. If the patient has missed more than one pill, she should not take the missed pills and they should be discarded. She should be advised to take the next pill at the next regular time and continue to take them as scheduled. Furthermore, she should use an additional method of contraception in addition to taking her pills for the remainder of the cycle.
- Use of oral contraceptives in the event of a missed menstrual period:

1. 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.
2. If the patient has adhered to the prescribed regimen and misses 2 consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.

### HOW SUPPLIED

Norminest® Fe Tablets (21 blue norethindrone 0.5 mg and ethinyl estradiol 0.035 mg tablets followed by 7 brown ferrous fumarate 75 mg tablets) and Norquest® Fe tablets (21 yellow-green norethindrone 1 mg and ethinyl estradiol 0.035 mg tablets followed by 7 brown ferrous fumarate 75 mg tablets) are available in 100 × 28 tablets blister packs.

CAUTION: Federal law prohibits dispensing without prescription.

### REFERENCES

1. Trussell, J., et al.: *Stud Fam Plann* 21(1):51-54, 1990. 2. Mann, J., et al.: *Br Med J* 2(5956):241-245, 1975. 3. Knopp, R.H.: *J Reprod Med* 31(9):913-921, 1986. 4. Mann, J.I., et al.: *Br Med J* 2:445-447, 1976. 5. Ory, H.: *JAMA* 237:2619-2622, 1977. 6. The Cancer and Steroid Hormone Study of the Centers for Disease Control: *JAMA* 249(2):1596-1599, 1983. 7. The Cancer and Steroid Hormone study of the Centers for Disease Control: *JAMA* 257(6):769-800, 1987. 8. Ory, H.W.: *JAMA* 228(1):68-69, 1974. 9. Ory, H.W., et al.: *N Engl J Med* 294:419-422, 1976. 10. Ory, H.W.: *Fam Plann Perspect* 14:182-184, 1982. 11. Ory, H.W., et al.: *Making Choices*, New York, The Alan Guttmacher Institute, 1983. 12. Stadel, B.: *N Engl J Med* 305(11):612-618, 1981. 13. Stadel, B.: *N Engl J Med* 305(12):672-677, 1981. 14. Adam, S., et al.: *Br J Obstet Gynaecol* 88:838-845, 1981. 15. Mann, J., et al.: *Br Med J* 2(5965):245-248, 1975. 16. Royal College of General Practitioners' Oral contraceptive Study: *Lancet* 1:541-546, 1981. 17. Slone, D., et al.: *N Engl J Med* 305(8):420-424, 1981. 18. Vessey, M.P.: *Br J Fam Plann* 6 (Supplement):1-12, 1980. 19. Russell-Briefel, R., et al.: *Prev Med* 15:352-362, 1986. 20. Goldbaum, G., et al.: *JAMA* 258(10):1339-1342, 1987. 21. LaRosa, J.C.: *J Reprod Med* 31 (9):906-912, 1986. 22. Krauss, R.M., et al.: *Am J Obstet Gynecol* 145:446-452, 1983. 23. Wahl, P., et al.: *N Engl J Med* 308(15):862-867, 1983. 24. Wynn, V., et al.: *Am J Obstet Gynecol* 142(6):766-771, 1982. 25. Wynn V., et al.: *J Reprod Med* 31(9):892-897, 1986. 26. Inman, W.H., et al.: *Br Med J* 2(5599): 193-199, 1968. 27. Maguire, M.G., et al.: *AM J Epidemiol* 110(2):188-195, 1979. 28. Petitti, D., et al.: *JAMA* 242(11):1150-1154, 1979. 29. Vessey, M.P., et al.: *Br Med J* 2(5599):199-205, 1968. 30. Vessey, M.P., et al.: *Br Med J* 2(5658):651-657, 1969. 31. Porter, J.B., et al.: *Obstet Gynecol* 59(3):299-302, 1982. 32. Vessey, M.P., et al.: *J Biosoc Sci* 8:373-427, 1976. 33. Mishell, D.R., et al.: *Reproductive Endocrinology*, Philadelphia, F.A. Davis co., 1979. 34. Petitti, D.B., et al.: *Lancet* 2:234-236, 1978. 35. Collaborative Group for the Study of Stroke in Young Women: *JAMA* 231(7):718-722, 1975. 36. Inman, W.H., et al.: *Br Med J* 2:203-209, 1970. 37. Meade, T.W., et al.: *Br Med J* 280(6224):1157-1161, 1980. 38. Kay, C.R.: *Am J Obstet Gynecol* 142(6):762-765, 1982. 39. Gordon, T., et al.: *Am J Med* 62:707-714, 1977. 40. Royal College of General Practitioners' Oral Contraception Study: *J Coll Gen Pract* 33:75-82, 1983. 41. Ory, H.W.: *Fam Plann Perspect* 15(2):57-63, 1983. 42. Paul, C., et al.: *Br Med J* 293: 723-725, 1986. 43. The Cancer and Steroid Hormone Study of the Centers for Disease Control: *N Engl J Med* 315(7):405-411, 1986. 44. Pike, M.C., et al.: *Lancet* 2:926-929, 1983. 45. Miller,

D.R., et al.: *Obstet Gynecol* 68:863-868, 1986. **46.** Olsson, H., et al.: *Lancet* 2:748-749, 1985. **47.** McPherson, K., et al.: *Br J Cancer* 56:653-660, 1987. **48.** Huggins, G.R., et al.: *Fertil Steril* 47(5):733-761, 1987. **49.** McPherson, K., et al.: *Br Med J* 293:709-710, 1986. **50.** Ory, H., et al.: *Am J Obstet Gynecol* 124(6):573-577, 1976. **51.** Vessey, M.P., et al.: *Lancet* 2:930, 1983. **52.** Brinton, L.A., et al.: *Int J Cancer* 38:339-344, 1986. **53.** WHO Collaborative Study of Neoplasia and Steroid Contraceptives: *Br Med J* 290:961-965, 1985. **54.** Rooks, J.B., et al.: *JAMA* 242(7):644-648, 1979. **55.** Bein, N.N., et al.: *Br J Surg* 64:433-435, 1977. **56.** Klatskin, G.: *Gastroenterology* 73:386-394, 1977. **57.** Henderson, B.E., et al.: *Br J Cancer* 48: 437-440, 1983. **58.** Neuberger, J., et al.: *Br Med J* 292:1355-1357, 1986. **59.** Forman, D., et al.: *Br Med J* 292:1357-1361, 1986. **60.** Harlap, S., et al.: *Obstet Gynecol* 55(4):447-452, 1980. **61.** Savolainen, E., et al.: *AM J Obstet Gynecol* 140(5):521-524, 1981. **62.** Janerich, D.T., et al.: *Am J Epidemiol* 112(1):73-79, 1980. **63.** Ferencz, C., et al.: *Teratology* 21:225-239, 1980. **64.** Rothman, K.J., et al.: *Am J Epidemiol* 109(4):433-439, 1979. **65.** Boston Collaborative Drug Surveillance Program: *Lancet* 1:1399-1404, 1973. **66.** Royal College of General Practitioners: *Oral Contraceptives and health*. New York, Pittman, 1974. **67.** Rome Group for the Epidemiology and Prevention of Cholelithiasis: *Am J Epidemiol* 119(5):796-805, 1984. **68.** Strom, B.L., et al.: *Clin Pharmacol Ther* 39(3):335-341, 1986. **69.** Perlman, J.A., et al.: *J Chronic Dis* 38(10):857-864, 1985. **70.** Wynn, V., et al.: *Lancet* 1:1045-1049, 1979. **71.** Wynn, V.: *Progesterone and Progestin*, New York, Raven Press, 1983. **72.** Wynn, V., et al.: *Lancet* 2:720-723, 1966. **73.** Fisch, I.R., et al.: *JAMA* 237(23):2499-2503, 1977. **74.** Laragh, J.H.: *Am J Obstet Gynecol* 126(1):141-147, 1976. **75.** Ramcharan, S., et al.: *Pharmacology of Steroid Contraceptive drugs*, New York, Raven Press, 1977. **76.** Stockley, I.: *Pharm J* 216:140-143, 1976. **77.** Dickey, R.P.: *Managing Contraceptive Pill Patients*, Oklahoma, Creative Informatics Inc., 1984. **78.** Porter J.B., Hunter J., Jick H., et al.: *Obstet Gynecol* 1985;66:1-4. **79.** Porter J.B., Hershel J., Walker A.M.: *Obstet Gynecol* 1987;70:29-32. **80.** Fertility and Maternal Health Drugs Advisory Committee, F.D.A., October, 1989. **81.** Schlesselman J., Stadel B.V., Murray P., Lai S.: *Breast Cancer in relation to early use of oral contraceptives*. *JAMA* 1988;259:1828-1833. **82.** Hennekens C.H., Speizer F.E., Lipnick R.J., Rosner B., Bain C., Belanger C., Stampfer M.J., Willett W., Peto R.: *A case-control study of oral contraceptive use and breast cancer*. *JNCI* 1984;72:39-42.



SYNTEX LABORATORIES, INC.  
PALO ALTO, CA 94304

LAB-1083-3.0  
Revised August 2017

## DETAILED PATIENT LABELING

### **Norminest® Fe Tablets**

(norethindrone and ethinyl estradiol)

### **Norquest® Fe Tablets**

(norethindrone and ethinyl estradiol)

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

#### INTRODUCTION

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

#### EFFECTIVENESS OF ORAL CONTRACEPTIVES

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

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

IUD: 3%

Diaphragm with spermicides: 18%

Spermicides alone: 21%

Vaginal sponge : 18 to 28%

Condom alone: 12%

Periodic abstinence: 20%

Injectable progestogen: 0.4%

Implants: 0.04%

No methods: 85%

## WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES

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

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

- A history of heart attack or stroke
- Blood clots in the legs (thrombophlebitis), brain (stroke), lungs (pulmonary embolism) or eyes
- A history of blood clots in the deep veins of your legs
- Chest pain (angina pectoris)
- Known or suspected breast cancer or cancer of the lining of the uterus, cervix or vagina.
- Unexplained vaginal bleeding (until a diagnosis is reached by your doctor)
- Yellowing of the whites of the eyes or of the skin (jaundice) during pregnancy or during previous use of the pill
- Liver tumor (benign or cancerous)
- Known or suspected pregnancy

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

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

### OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

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

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

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

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

## **RISKS OF TAKING ORAL CONTRACEPTIVES**

### **1. Risk of developing blood clots**

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

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

### **2. Heart attacks and strokes**

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

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

### **3. Gallbladder disease**

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

### **4. Liver tumors**

In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, a possible but not definite association has been found with the pill and liver cancers in 2 studies in which a few women who developed these very rare cancers were found to have used oral contraceptives for long periods. However, liver cancers are extremely rare.

### **5. Cancer of the breast and reproductive organs**

There is, at present, no confirmed evidence that oral contraceptives increase the risk of cancer of the reproductive organs in human studies. Several studies have found no overall increase in the risk of developing breast cancer. However, women who use oral contraceptives and have a strong family history of breast cancer or who have breast nodules or abnormal mammograms should be followed closely by their doctors. Some studies have reported an increase in the risk of developing breast cancer, particularly at a younger age. This increased risk appears to be related to duration of use.

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

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

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

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

\*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 from the table that for women aged 15 to 39 the risk of death is highest with pregnancy (7-26 deaths per 100,000 women, depending on age). Among pill users who do not smoke the risk of death is always lower than that associated with pregnancy for any age group, although over the age of 40 the risk increases to 32 deaths per 100,000 women compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35 the estimated number of deaths exceeds those for the other methods of birth control. If a woman is over the age of 40 and smokes, her estimated risk of death is 4 times higher (117/100,000 women) than the estimated risk associated with pregnancy (28/100,000 women) in that age group.

The suggestion that women over 40 who don't smoke should not take oral contraceptives is based on information from older high-dose pills and on less selective use of pills than is practiced today. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of oral contraceptive use by healthy, non-smoking women over 40 years of age may outweigh the possible

risks. However, all women, especially older women, are cautioned to use the lowest dose pill that is effective.

### **WARNING SIGNALS**

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

- Sharp chest pain, coughing of blood or sudden shortness of breath (indicating a possible clot in the lung)
- Pain in the calf ( indicating a possible clot in the leg)
- Crushing chest pain or heaviness in the chest (indicating a possible heart attack)
- Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness or numbness in an arm or leg (indicating a possible stroke)
- Sudden partial or complete loss of vision (indicating a possible clot in the eye)
- Breast lumps (indicating possible breast cancer or fibrocystic disease of the breast: ask your doctor or health care provider to show you how to examine your breasts)
- Severe pain or tenderness in the stomach area (indicating a possible ruptured liver tumor)
- Difficulty in sleeping, weakness, lack of energy, fatigue or change in mood (possibly indicating severe depression)
- Jaundice or yellowing of the skin or eyeballs, accompanied frequently by fever, fatigue, loss of appetite, dark colored urine or light colored bowel movements (indicating possible liver problems)

### **SIDE EFFECTS OF ORAL CONTRACEPTIVES**

#### **1. Vaginal bleeding**

Irregular vaginal bleeding or spotting may occur while you are taking the pill. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problem. It is important to continue taking your pills on schedule. If the bleeding occurs in more than 1 cycle or lasts for more than a few days, talk to your doctor or health care provider.

#### **2. Contact lenses**

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

#### **3. Fluid retention**

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

#### **4. Melasma (Mask of Pregnancy)**

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

## **5. Other side effects**

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

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

## **GENERAL PRECAUTIONS**

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

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

There is no conclusive evidence that oral contraceptives use is associated with an increase in birth defects when taken inadvertently during early pregnancy. Previously, a few studies had reported that oral contraceptives might be associated with birth defects but these studies have not been confirmed. Nevertheless, oral contraceptives or any other drugs should not be used during pregnancy unless clearly necessary and prescribed by your doctor. You should check with your doctor about risks to your unborn child from any medication taken during pregnancy.

### **2. While breast feeding**

If you are breast feeding, consult your doctor before starting oral contraceptives. Some of the drug will be passed on to the child in the milk. A few adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. In addition, oral contraceptives may decrease the amount and quality of your milk. If possible, use another method of contraception while breast feeding. You should consider starting oral contraceptives only after you have weaned your child completely.

### **3. Laboratory tests**

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

### **4. Drug interactions**

Certain drugs may interact with birth control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Such drugs include rifampin; drugs used for epilepsy such as barbiturates (for example phenobarbital) and phenytoin (Dilantin is one brand of this drug); phenylbutazone (Butazolidin is one brand of this drug) and possibly certain antibiotics. You may need to use additional contraception when you take drugs which can make oral contraceptives less effective.

## HOW TO TAKE ORAL CONTRACEPTIVES

### 1. Important points to remember

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.

Before you start taking your pills:

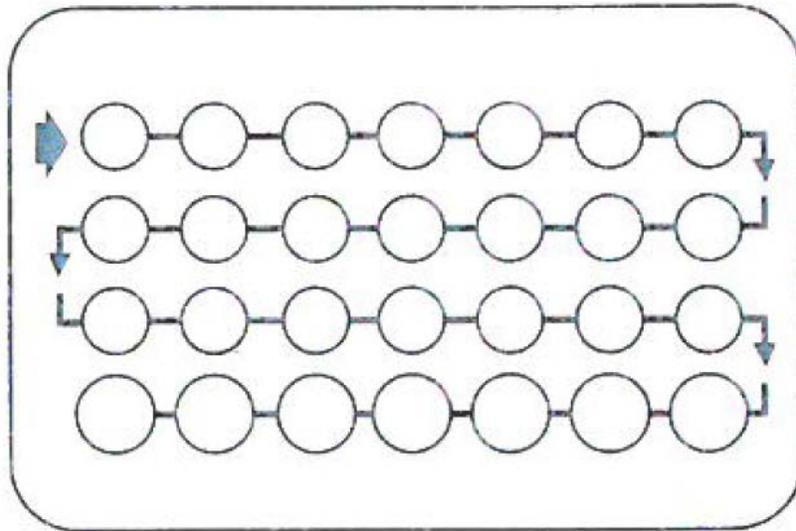
- Be sure to read these directions:  
Before you start taking your pills.  
Any time you are not sure what to do.
- The right way to take the Pill is to take one pill every day at the same time. If you miss pills you could get pregnant. The more pills you miss, the more likely you are to get pregnant.
- Many women have spotting or light bleeding while they are taking the Pill, or may feel sick to their stomachs during the first 1-3 packs of Pills. If you feel sick to your stomach, do not stop taking the Pill. These problems will usually go away after the first three months. If they do not go away, talk to your doctor or clinic.
- Missing pills can also cause spotting or light bleeding (see the section on MISSED PILLS). You could also feel a little sick to your stomach on the days you take a missed pill with your regularly scheduled pill.
- If you have vomiting or diarrhea, for any reason, or if you take some medicines, including some antibiotics, your pills may not work as well. Use a back-up method of birth control until you check with your doctor or clinic. Talk to your doctor or clinic about which back-up birth control method is right for you.
- If you have trouble remembering to take the pill (for example, if you forget to take more than one pill two months in a row), talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.
- If you have any questions or are unsure about the information in this leaflet, call your doctor or clinic.

### 2. Before you start taking your pills

- Decide what time of day you want to take your pill. It is important to take it at about the same time every day.
- Look at your pill pack to see if it has 28 pills:  
The 28-pill pack has 21 “active” blue or yellow-green pills (with hormones) to take for 3 weeks, followed by 1 week of “reminder” brown pills (without hormones).
- Also find:
  - 1) where on the pack to start taking pills,
  - 2) in what order to take the pills (follow the arrows) and
  - 3) the days of the week as shown on the pill card.

**Active Pill Colors: Blue or Yellow-Green**

**Reminder Pill Color: Brown**



- Be sure you have ready at all times:
  - Another kind of birth control to use as a back-up in case you miss pills. (Remember to talk to your doctor or clinic about an appropriate back-up method of birth control for you.)
  - An extra, full pill pack.

### **3. When to start the first pack of pills**

You have a choice of which day to start taking your first pack of pills (Sunday or Day 5 of your period). Decide with your doctor or clinic which is the best day for you to start. Pick a time of day which will be easy to remember.

#### **Sunday Start:**

- Take the first pill of the first pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, take your first pill of the first pack that same day.
- Use another method of birth control as a back-up method if you have sex any time from the Sunday you start your first pack until the next Sunday (7 days). Talk to your doctor about an appropriate back-up method of birth control for you.

#### **Day 5 Start:**

- Count the first day of your period as Day 1. Take the first pill of the first pack on the fifth day of your period, even if you are still bleeding.
- Use another method of birth control as a back-up method if you have sex any time during the 7 days after you take your first pill. Talk to your doctor or clinic about an appropriate back-up method of birth control for you.

#### 4. What to do during the month

- **Take one pill at the same time every day until the pack is empty.**

Do not skip pills even if you are spotting or have light bleeding between monthly periods or feel sick to your stomach (nausea).

Do not skip pills even if you do not have sex very often.

- **When you finish a pack of pills:**

Start the next pack on the day after your last “reminder” pill. Do not wait any days between packs.

#### 5. What to do if you miss pills

If you **MISS 1** “active” blue or yellow-green pill:

- Take it as soon as you remember. Take the next pill at your regular time. This means you take 2 pills in 1 day.
- Missing a pill can cause spotting or light bleeding. You could also feel a little sick to your stomach on the days you take a missed pill with your regularly scheduled pill.
- You do not need to use a back-up birth control method if you have sex.

If you **MISS MORE THAN 1** “active” blue or yellow-green pill in a row:

- Do not take the missed pills. The missed pills may be discarded. Take the next pill at your regular time. Continue to take one pill a day as scheduled.
- Missing pills can cause spotting or light bleeding.
- You **MAY BECOME PREGNANT**, especially if you sex in the first 7 days after you have missed pills. Therefore, you **MUST** use a back-up method of birth control until you start a new pill pack. (Remember to talk to your doctor or clinic about an appropriate back-up birth control method for you.)

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

THROW AWAY the pills you missed.

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

You do not need a back-up method of birth control during this time.

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

Use a **BACK-UP METHOD OF BIRTH CONTROL** anytime you have sex.

**KEEP TAKING ONE PILL EACH DAY** until you can talk to your doctor or clinic.

#### 6. Missed periods, spotting or light bleeding

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

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

### **7. Stopping the pill before surgery or prolonged bed rest**

If you are scheduled for surgery or you need to stay in bed for a long period of time you should tell your doctor that you are on the Pill. You should stop taking the Pill 4 weeks before your operation to avoid an increased risk of blood clots. Talk to your doctor about when you may start taking the Pill again.

### **8. Starting the pill after pregnancy**

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

### **9. Pregnancy due to pill failure**

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

### **10. Pregnancy after stopping the pill**

There may be some delay in becoming pregnant after you stop taking the Pill, especially if you had irregular periods before you started using the pill. Your doctor may recommend that you delay becoming pregnant until you have had one or more regular periods.

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

### **11. Overdosage**

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

### **12. Other information**

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

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

If you want more information about birth control pills, ask your doctor or clinic. They have a more technical leaflet called **PHYSICIAN LABELING** which you might want to read.

### **NON-CONTRACEPTIVE HEALTH BENEFITS**

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

- Menstrual cycles may become more regular
- Blood flow during menstruation may be lighter and less iron may be lost.

Therefore, anemia due to iron deficiency is less likely to occur.

- Pain or other symptoms during menstruation may be encountered less frequently
- Ectopic (tubal) pregnancy may occur less frequently
- Non-cancerous cysts or lumps in the breast may occur less frequently
- Acute pelvic inflammatory disease may occur less frequently
- Oral contraceptive use may provide some protection against developing two forms of cancer: cancer of the ovaries and cancer of the lining of the uterus

Store at controlled room temperature 15-30<sup>0</sup>C (59-86<sup>0</sup>F).



SYNTEX LABORATORIES, INC.  
PALO ALTO, CA 94304

LAB-1084-2.0

Revised October 2017

**BRIEF SUMMARY**  
**PATIENT PACKAGE INSERT**

**Norminest® Fe Tablets**

(norethindrone and ethinyl estradiol)

**Norquest® Fe Tablets**

(norethindrone and ethinyl estradiol)

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

Oral contraceptives, also known as “birth control pills” or “the pill,” are taken to prevent pregnancy and, when taken correctly, have a failure rate of about 1% per year when used without missing any pills. The typical failure rate of large numbers of pill users is less than 3% per year when women who miss pills are included. For most women, oral contraceptives are also free of serious or unpleasant side effects. However, forgetting to take oral contraceptives considerably increases the chances of pregnancy.

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

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

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

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

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

Most side effects of the pill are not serious. The most common such effects are nausea, vomiting, bleeding between menstrual periods, weight gain, breast tenderness and difficulty wearing contact lenses. These side effects, especially nausea and vomiting, may subside within the first 3 months of use.

The serious side effects of the pill occur very infrequently, especially if you are in good health and are young. However, you should know that the following medical conditions have been associated with or made worse by the pill:

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

The symptoms associated with these serious side effects are discussed in the detailed leaflet given to you with your supply of pills. Notify your doctor or health care provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anti-convulsants and some antibiotics, may decrease oral contraceptive effectiveness.

Studies to date of women taking the pill have not shown an increase in the incidence of cancer of the breast or cervix. There is, however, insufficient evidence to rule out the possibility that the pill may cause such cancers. Some studies have reported an increase in the risk of developing breast cancer, particularly at a younger age. This increased risk appears to be related to duration of use.

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

Be sure to discuss any medical condition you may have with your health care provider. Your health care provider will take a medical and family history before prescribing oral contraceptives and will examine you. You should be reexamined at least once a year while taking oral contraceptives. The detailed patient information leaflet gives you further information which you should read and discuss with your health care provider.

#### **HOW TO TAKE ORAL CONTRACEPTIVES**

*See full text of How To Take Oral Contraceptives which is printed in full in the Detailed Patient Labeling.*



LAB-1085-2.0  
Revised October 2017