SUMMARY OF PRODUCT CHARACTERISTICS

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Fam Care
Levonorgestrel and Ethinyl Estradiol Tablets USP, 0.15 mg/0.03 mgwith Ferrous Fumarate Tablets 75 mg

1. NAME OF THE MEDICINAL PRODUCT

Fam Care

Levonorgestrel and Ethinyl Estradiol Tablets USP, 0.15 mg/0.03 mg with Ferrous FumarateTablets 75 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Levonorgestrel
USP……0.15 mgEthinyl Estradiol
USP..... 0.03 mg
Excipients ..... q.s. (21 tablets)

Each tablet contains:
Ferrous Fumarate USP……75mg
Excipients ..... q.s. (7 Tablets)

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Oral Tablets

Light Orange Active Tablets (21 Per Blister)

Light orange color, round, uncoated tablets debossed with 'EF1' on one side and plain on other side, tablets may have mottled appearance on either of the surface.

Brown Mottled Tablets Hormone Free Tablets (7 Per Blister)

Brown, round, flat faced beveled edge, uncoated tablets debossed with ‘EJ2’ on one side andplain on other side; tablets may have mottled appearance on either of surface.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Levonorgestrel and Ethinyl Estradiol tablets are indicated for use by females of reproductive potential to prevent pregnancy.

4.2 Posology and method of administration

Method of administration

Oral use

Dosage regimen

How to Start and Take Levonorgestrel and Ethinyl Estradiol Tablets

Levonorgestrel and Ethinyl Estradiol tablets are dispensed in a compact dispenser containing28 tablets (see section 6.7). Levonorgestrel and Ethinyl Estradiol tablets may be startedusing either a Day 1 start or a Sunday start (see Table 1). For the first cycle of a Sunday start regimen, an additional method of contraception should be used until after the first 7 consecutive days of administration.

Table 1: Instructions for Administration of Levonorgestrel and Ethinyl Estradiol Tablets

Starting Levonorgestrel and Ethinyl Estradiol tablets in females with no current use of hormonal contraception	Day 1 start • Take first tablet without regard to meals on the first day of menses • Take subsequent tablets once daily at the same time each day • Begin each subsequent pack on the same day of the week as the first cycle pack (i.e., on the day after taking the last tablet)
	Sunday start • Take first tablet without regard to meals on the first Sunday after the onset of menstrual period • Take subsequent tablets once daily at the same time each day • Use additional nonhormonal contraception for the first seven days of product use • Begin each subsequent pack on the same day of the week as the first cycle pack (i.e., on the day after taking the last tablet)
Switching from another contraceptive method • **A COC**	Start Levonorgestrel and Ethinyl Estradiol tablets: • On the day when the new pack of the previous COC would have been started
• **Transdermal patch**	• On the day when next application would have been scheduled
• **Vaginal ring**	• On the day when next insertion would have been scheduled
• **Injection**	• On the day when next injection would have been scheduled
• **Intrauterine contraceptive**	• On the day of removal
• **Implant**	• On the day of removal

Starting Levonorgestrel and Ethinyl Estradiol tablets after Abortion or Miscarriage

First-trimester

- After a first-trimester abortion or miscarriage, Levonorgestrel and Ethinyl Estradiol tablets may be started immediately. An additional method of contraception is not needed if Levonorgestrel and Ethinyl Estradiol tablets are started immediately.
- If Levonorgestrel and Ethinyl Estradiol tablets are not started within 5 days after termination of the pregnancy, the patient should use additional non-hormonal contraception (such as condoms or spermicide) for the first seven days of her first cycle of Levonorgestrel and Ethinyl Estradiol tablets.

Second-trimester

- Do not start until 4 weeks after a second-trimester abortion or miscarriage, due to the increased risk of thromboembolic disease. Start Levonorgestrel and Ethinyl Estradiol tablets following the instructions in Table 3 for Day 1 or Sunday start. Use additional non-hormonal contraception (such as condoms or spermicide) for the first seven days of the patient's first cycle of levonorgestrel and ethinyl estradiol tablets (see Contraindications, Special warnings and precautions for use).

Starting Levonorgestrel and Ethinyl Estradiol Tablets after Childbirth

- Do not start until 4 weeks after delivery, due to the increased risk of thromboembolic disease. Start contraceptive therapy with Levonorgestrel and Ethinyl Estradiol tablets following the instructions in Table 1 for women not currently using hormonal contraception.
- Levonorgestrel and ethinyl estradiol tablets are not recommended for use in lactating women (see special warnings and precautions for use).
- If the woman has not yet had a period postpartum, consider the possibility of ovulation and conception occurring prior to use of Levonorgestrel and Ethinyl Estradiol tablets (see Contraindications, Special warnings and precautions for use).

Dosing Levonorgestrel and Ethinyl Estradiol tablets

Instruct patients to take one tablet by mouth at the same time every day. To achievemaximum contraceptive effectiveness, patients must take Levonorgestrel and Ethinyl Estradiol tablets as directed, in the order directed on the blister pack. The failure rate may increase when pills are missed or taken incorrectly.

Missed doses

Instruct patients about the handling of missed doses (e.g., to take single missed pills as soon as possible).

Table 2: Instructions for Missed Levonorgestrel and Ethinyl Estradiol Tablets

• If one active tablet is missed in Weeks 1, 2, or 3	Take the tablet as soon as possible. Continue taking one tablet a day until the pack is finished.
• If two active tablets are missed in Week 1 or	Take the two missed tablets as soon as possible andthe next two active tablets the next day. Continue

Week 2	taking one tablet a day until the pack is finished. **Additional nonhormonal contraception (such as condoms or spermicide) should be used as back- up if the patient has sex within 7 days after missing tablets.**
• If two active tablets are missed in the third week or three or more active tablets are missed in a row in Weeks 1, 2, or 3	Day 1 start: Throw out the rest of the pack and start a new pack that same day. Sunday start: Continue taking one tablet a day until Sunday, then throw out the rest of the pack and starta new pack that same day. **Additional nonhormonal contraception (such as condoms or spermicide) should be used as back- up if the patient has sex within 7 days after missing tablets.**

Advice in Case of Gastrointestinal Disturbances

If vomiting occurs within 3 to 4 hours after taking Levonorgestrel and Ethinyl Estradiol tablets, the patient should proceed as if she missed a tablet. In case of prolonged vomiting or diarrhea, absorption may not be complete and additional contraceptive measures should be taken.

Additional information on special populations

Pediatric use:
Safety and efficacy of levonorgestrel and ethinyl estradiol tablets have been established in females of reproductive potential. Use of levonorgestrel and ethinyl estradiol tablets before menarche is not indicated.

Geriatric patients:
Levonorgestrel and ethinyl estradiol tablets has not been studied in postmenopausal women and is not indicated in this population.

4.3 Contraindications

Levonorgestrel and Ethinyl Estradiol tablets are contraindicated in females who are known to have the following conditions:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35
  - Have current or history of deep vein thrombosis or pulmonary embolism
  - Have cerebrovascular disease
  - Have coronary artery disease
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation)
  - Have inherited or acquired hypercoagulopathies
  - Have uncontrolled hypertension or hypertension with vascular disease
  - Have diabetes mellitus and are over age 35, diabetes mellitus with hypertension or vascular disease or other end-organ damage, or diabetes mellitus of >20 years duration

  - Have headaches with focal neurological symptoms, migraine headaches with aura, or over age 35 with any migraine headaches
- Current diagnosis of, or history of, breast cancer, which may be hormone-sensitive
- Liver tumors, acute viral hepatitis, or severe (decompensated) cirrhosis
- Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations
- Undiagnosed abnormal uterine bleeding

For further details see section 4.4

4.4 Special warnings and precautions for use Thromboembolic

Disorders and Other Vascular Conditions

- Stop Levonorgestrel and Ethinyl Estradiol tablets if an arterial or venous thrombotic/thromboembolic event occurs.
- Stop Levonorgestrel and Ethinyl Estradiol tablets if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions and evaluate for retinal vein thrombosis immediately.
- Discontinue Levonorgestrel and Ethinyl Estradiol tablets during prolonged immobilization. If feasible, stop Levonorgestrel and Ethinyl Estradiol tablets at least four weeks before and through two weeks after major surgery, or other surgeries known to have an elevated risk of thromboembolism.
- Start Levonorgestrel and Ethinyl Estradiol tablets no earlier than four weeks after delivery in females who are not breast-feeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the likelihood of ovulation increases after the third postpartum week.
- Before starting Levonorgestrel and Ethinyl Estradiol tablets evaluate any past medical history or family history of thrombotic or thromboembolic disorders and consider whether the history suggests an inherited or acquired hypercoagulopathy. Levonorgestrel and Ethinyl Estradiol tablets are contraindicated in females with a high risk of arterial or venous thrombotic/thromboembolic diseases (see Contraindications).

Arterial Events

COCs increase the risk of cardiovascular events and cerebrovascular events, such as myocardial infarction and stroke. The risk is greater among older women (> 35 years of age), smokers, and females with hypertension, dyslipidemia, diabetes, or obesity.

Levonorgestrel and Ethinyl Estradiol tablets are contraindicated in women over 35 years of age who smoke (see Contraindications). Cigarette smoking increases the risk of serious cardiovascular events from COC use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked.

Venous Events

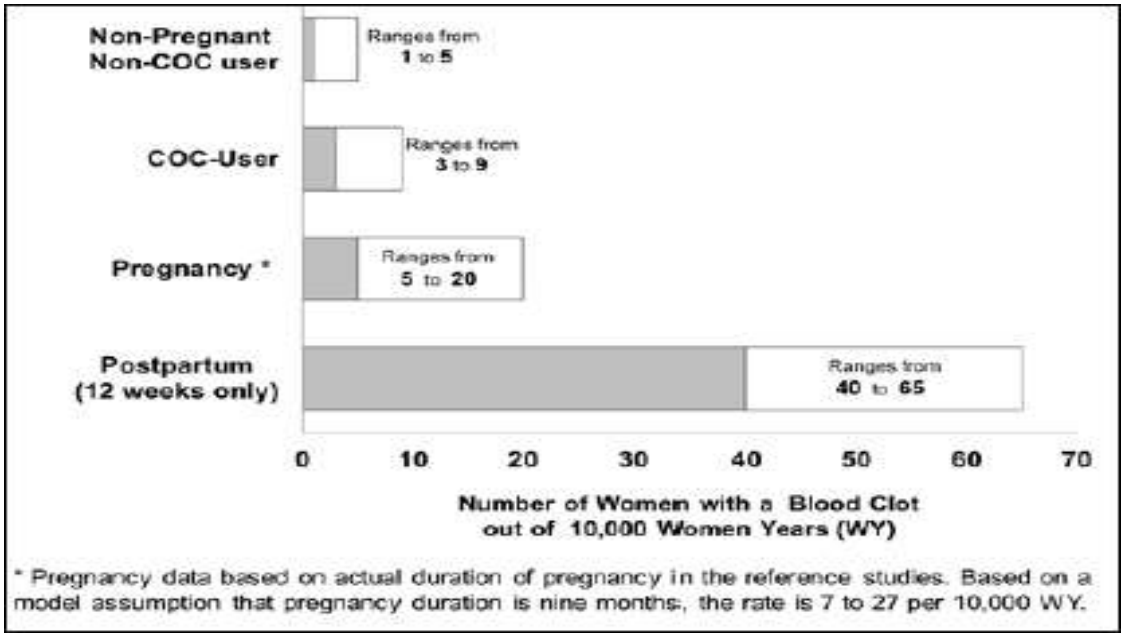
Use of COCs increases the risk of venous thromboembolic events (VTEs), such as deep vein thrombosis and pulmonary embolism. Risk factors for VTEs include smoking, obesity, and family history of VTE, in addition to other factors that contraindicate use of COCs (see Contraindications). While the increased risk of VTE associated with use of COCs is well-

established, the rates of VTE are even greater during pregnancy, and especially during the postpartum period (see Figure 1). The rate of VTE in females using COCs has been estimatedto be 3 to 9 cases per 10,000 woman-years.

The risk of VTE is highest during the first year of use of a COC and when restarting hormonal contraception after a break of four weeks or longer. Based on results from a few studies, there is some evidence that this is true for non-oral products as well. The risk of thromboembolic disease due to COCs gradually disappears after COC use is discontinued.

Figure 1 shows the risk of developing a VTE for females who are not pregnant and do not use oral contraceptives, for females who use oral contraceptives, for pregnant females, and for females in the postpartum period. To put the risk of developing a VTE into perspective: If 10,000 females who are not pregnant and do not use oral contraceptives are followed for one year, between 1 and 5 of these females will develop a VTE.

Figure 1: Likelihood of Developing a VTE



Liver Disease

Elevated Liver Enzymes

Levonorgestrel and Ethinyl Estradiol tablets are contraindicated in females with acute viral hepatitis or severe (decompensated) cirrhosis of liver (see contraindications). Discontinue Levonorgestrel and Ethinyl Estradiol tablets if jaundice develops. Acute liver testabnormalities may necessitate the discontinuation of COC use until the liver tests return to normal and COC causation has been excluded.

Liver Tumors

Levonorgestrel and Ethinyl Estradiol tablets are contraindicated in females with benign or malignant liver tumors (see Contraindications). COCs increase the risk of hepatic adenomas. An estimate of the attributable risk is 3.3 cases/100,000 COC users. Rupture of hepatic

adenomas may cause death from abdominal haemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (> 8 years) COC users. The attributable risk of liver cancers in COC users is less than one case per million users.

Malignant Neoplasms

Breast Cancer
Levonorgestrel and ethinyl estradiol tablet is contraindicated in women 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 lastuse) and current users with longer duration of COC use.

Cervical Cancer
Some studies suggest that COCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. There is controversy about the extent to which these findings are due to differences in sexual behavior and other factors.

Hypertension

Levonorgestrel and Ethinyl Estradiol tablets are contraindicated in females with uncontrolled hypertension or hypertension with vascular disease (see Contraindications). For all females, including those with well-controlled hypertension, monitor blood pressure at routine visits and stop Levonorgestrel and Ethinyl Estradiol tablets if blood pressure rises significantly.

An increase in blood pressure has been reported in females using COCs, and this increase is more likely in older women with extended duration of use. The effect of COCs on blood pressure may vary according to the progestin in the COC.

Age-related Considerations

The risk for cardiovascular disease and prevalence of risk factors for cardiovascular disease increase with age. Certain conditions, such as smoking and migraine headache without aura, that do not contraindicate COC use in younger females, are contraindications to use in women over 35 years of age (see Contraindications, Special warnings and precautions for use). Consider the presence of underlying risk factors that may increase the risk of cardiovascular disease or VTE, particularly before initiating a COC for women over 35 years, such as:

- Hypertension
- Diabetes
- Dyslipidemia
- Obesity

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 levonorgestrel and ethinyl estradiol tablets prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (see Contraindications). Levonorgestrel and Ethinyl Estradiol tablets can be restarted approximately 2 weeks following completion of treatment with the combination drug regimen.

Gallbladder Disease

Studies suggest an increased risk of developing gallbladder disease among COC users. Use of COCs may also worsen existing gallbladder disease.

A past history of COC-related cholestasis predicts an increased risk with subsequent COC use. Females with a history of pregnancy-related cholestasis may be at an increased risk for COC-related cholestasis.

Adverse Carbohydrate and Lipid Metabolic Effects

Hyperglycemia
Levonorgestrel and Ethinyl Estradiol tablets are contraindicated in diabetic women over age 35, or females who have diabetes with hypertension, nephropathy, retinopathy, neuropathy, other vascular disease, or females with diabetes of > 20 years duration (see Contraindications). Levonorgestrel and ethinyl estradiol tablets may decrease glucose tolerance. Carefully monitor prediabetic and diabetic females who are using Levonorgestrel and Ethinyl Estradiol tablets.

Dyslipidemia
Consider alternative contraception for females with uncontrolled dyslipidemia. Levonorgestrel and Ethinyl Estradiol tablets may cause adverse lipid changes.
Females with hypertriglyceridemia, or a family history thereof, may have an increase in serum triglyceride concentrations when using Levonorgestrel and Ethinyl Estradiol tablets, which may increase the risk of pancreatitis.

Headache

Levonorgestrel and Ethinyl Estradiol tablets are contraindicated in females who have headaches with focal neurological symptoms or have migraine headaches with aura, and in women over age 35 years who have migraine headaches with or without aura (see Contraindications).
If a woman using Levonorgestrel and Ethinyl Estradiol tablets develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Levonorgestrel and Ethinyl Estradiol tablets if indicated. Consider discontinuation of Levonorgestrel and Ethinyl Estradiol tablets if there is an increased frequency or severity of migraines during COC use (which may be prodromal of a cerebrovascular event).

Bleeding Irregularities and Amenorrhea

Unscheduled Bleeding and Spotting

Females using Levonorgestrel and Ethinyl Estradiol tablets may experience unscheduled (breakthrough or intracyclic) bleeding and spotting, especially during the first three monthsof use. Bleeding irregularities may resolve over time or by changing to a different contraceptive product. If bleeding persists or occurs after previously regular cycles, evaluate for causes such as pregnancy or malignancy.

In two clinical trials of Levonorgestrel and Ethinyl Estradiol (1084 subjects reporting for a total of 8186 treatment cycles and 238 subjects reporting for a total of 1102 treatment cycles), breakthrough bleeding occurred in 6.9% and 8.1% of reported cycles, and spotting occurredin 8.6% and 7.9% of reported cycles over the total study duration, respectively. In the two trials, intermenstrual bleeding (i.e., breakthrough bleeding and/or spotting) occurred in 13.1% and 12.9% of reported cycles over the total study duration, respectively. In one trial, 33 subjects out of 1084 (3.0%) discontinued due to bleeding irregularities (i.e., breakthrough bleeding and spotting); in the other trial, 6 subjects out of 238 (2.5%) discontinued due to bleeding irregularities.

Amenorrhea and Oligomenorrhea

Females who use Levonorgestrel and Ethinyl Estradiol tablets may experience absence of scheduled (withdrawal) bleeding, even if they are not pregnant. In two clinical trials of Levonorgestrel and ethinyl estradiol, one including 8186 reported treatment cycles, and the other including 1102 reported treatment cycles, amenorrhea occurred in 1.5% of treatment cycles in each trial.

If scheduled bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or two active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and perform appropriate diagnostic measures. If the patient hasadhered to the prescribed dosing schedule and misses two consecutive periods, rule out pregnancy.

After discontinuation of a COC, amenorrhea or oligomenorrhea may occur, especially if these conditions were pre-existent.

Depression

Carefully observe females with a history of depression and discontinue Levonorgestrel and Ethinyl Estradiol tablets if depression recurs to a serious degree. Data on the association of COCs with onset of depression or exacerbation of existing depression are limited.

Effect on Binding Globulins

The estrogen component of Levonorgestrel and Ethinyl Estradiol tablets may raise the serum concentrations of thyroxine-binding globulin, sex hormone-binding globulin, and cortisol-binding globulin. The dose of replacement thyroid hormone or cortisol therapy may need to be increased.

Hereditary Angioedema

In females with hereditary angioedema, exogenous estrogens may induce or exacerbatesymptoms of angioedema.

Chloasma

Chloasma may occur with Levonorgestrel and Ethinyl Estradiol tablets use, especially in females with a history of chloasma gravidarum. Advise females with a history of chloasma to avoid exposure to the sun or ultraviolet radiation while using Levonorgestrel and Ethinyl Estradiol tablets.

Precautions

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.

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

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.

Gastrointestinal Motility

Diarrhea and/or vomiting may reduce hormone absorption.

4.5 Interaction with other medicinal products and other forms of interactions

The sections below provide information on substances for which data on drug interactions with Combined Oral Contraceptives are available. There is little information available about the clinical effect of most drug interactions that may affect COCs. However, based on the known pharmacokinetic effects of these drugs, clinical strategies to minimize any potential adverse effect on contraceptive effectiveness or safety are suggested.

Consult the approved product labeling of all concurrently used drugs to obtain further information about interactions with COCs or the potential for metabolic enzyme or transporter system alterations**.**

No drug-drug interaction studies were conducted with Levonorgestrel and Ethinyl Estradiol tablets.

Effects of Other Drugs on Combined Oral Contraceptives

Substances Decreasing the Plasma Concentrations of COCs and Potentially Diminishing the Efficacy of COCs:

Table 3 includes substances that demonstrated an important drug interaction withlevonorgestrel and ethinyl estradiol tablets.

Table 3: Significant Drug Interactions Involving Substances That Affect COCs

Metabolic Enzyme Inducers	
Clinical effect	• Concomitant use of COCs with metabolic enzyme inducers may decrease the plasma concentrations of the estrogen and/or progestin component of COCs. • Decreased exposure of the estrogen and/or progestin component of COCs may potentially diminish the effectiveness of COCs and may lead to contraceptive failure or an increase in breakthrough bleeding.
Prevention or management	• Counsel females to use an alternative method of contraception or a backup method when enzyme inducers are used with COCs. • Continue backup contraception for 28 days after discontinuing the enzyme inducer to maintain contraceptive reliability.
Examples	Aprepitant, barbiturates, bosentan, carbamazepine, efavirenz, felbamate, griseofulvin, oxcarbazepine, phenytoin, rifampin, rifabutin, rufinamide, topiramate, products containing St. John's wort[a], and certain protease inhibitors.
Colesevelam	
Clinical effect	• Concomitant use of COCs with colesevelam significantly decreases systemic exposure of ethinyl estradiol. • Decreased exposure of the estrogen component of COCs may potentially reduce contraceptive efficacy or result in an increase in breakthrough bleeding, depending on the strength of ethinyl estradiol in the COC.
Prevention or management	Administer 4 or more hours apart to attenuate this drug interaction.

[a] Induction potency of St. John's wort may vary widely based on preparation.

Substances increasing the systemic exposure of COCs:

Co-administration of atorvastatin or rosuvastatin and COCs containing Ethinyl Estradiol increase systemic exposure of Ethinyl Estradiol by approximately 20 to 25 percent. Ascorbic acid and acetaminophen may increase systemic exposure of Ethinyl Estradiol, possibly by inhibition of conjugation. CYP3A inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase systemic exposure of the estrogen and/or progestin component of COCs.

Human immunodeficiency virus (HIV)/hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors:

Significant decreases in systemic exposure of the estrogen and/or progestin have been noted when COCs are co-administered with some HIV protease inhibitors (e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos) amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir), some HCV protease inhibitors (e.g., boceprevir and telaprevir), and some non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine).

In contrast, significant increases in systemic exposure of the estrogen and/or progestin have been noted when COCs are co-administered with certain other HIV protease inhibitors (e.g., indinavir and atazanavir/ritonavir) and with other non-nucleoside reverse transcriptase inhibitors (e.g., etravirine).

Effects of Combined Oral Contraceptives on Other Drugs

Table 4 provides significant drug interaction information for drugs co-administered with Levonorgestrel and Ethinyl Estradiol tablets.

Table 4: Significant Drug Interaction Information for Drugs Co-Administered with COCs

Lamotrigine	
Clinical effect	• Concomitant use of COCs with lamotrigine may significantly decrease systemic exposure of lamotrigine due to induction of lamotrigine glucuronidation. • Decreased systemic exposure of lamotrigine may reduce seizure control.
Prevention or management	Dose adjustment may be necessary. Consult the approved product labeling for lamotrigine.
Thyroid Hormone Replacement Therapy or Corticosteroid Replacement Therapy	
Clinical effect	Concomitant use of COCs with thyroid hormone replacement therapy or corticosteroid replacement therapy may increase systemic exposure of thyroid-binding and cortisol-binding globulin
Prevention or management	The dose of replacement thyroid hormone or cortisol therapy may need to be increased. Consult the approved product labeling for the therapy in use.
Other Drugs	
Clinical effect	Concomitant use of COCs may decrease systemic exposure of acetaminophen, morphine, salicylic acid, and temazepam. Concomitant use with ethinyl estradiol-containing COCs may increase systemic exposure of other drugs (e.g., cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole).
Prevention or management	The dosage of drugs that can be affected by this interaction may need to be increased. Consult the approved product labeling for the concomitantly used drug.

Concomitant Use with Hepatitis C Virus (HCV) Combination Therapy –Liver Enzyme Elevation

Do not co-administer Levonorgestrel and Ethinyl Estradiol Tablets with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, and glecaprevir/pibrentasvir due to potential for ALT elevations.

Effect on Laboratory Tests

The use of COCs may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk Summary

Discontinue Levonorgestrel and Ethinyl Estradiol tablets if pregnancy occurs because thereis no reason to use COCs in pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or nongenital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to COCs before conception or during early pregnancy. Animal studies to evaluate embryo/fetal toxicity were not conducted.

Lactation

Risk Summary

Contraceptive hormones and/or metabolites are present in human milk. COCs can reduce milk production in breast-feeding females. This reduction can occur at any time but is less likely to occur once breast-feeding is well-established. When possible, advise the nursing female to use other methods of contraception until she discontinues breast-feeding. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for levonorgestrel and ethinyl estradiol tablets and any potential adverse effects on the breast-fed child from Levonorgestrel and Ethinyl Estradiol tablets or from the underlying maternal condition

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Noeffects on ability to drive and use machines have been observed in users of COCs.

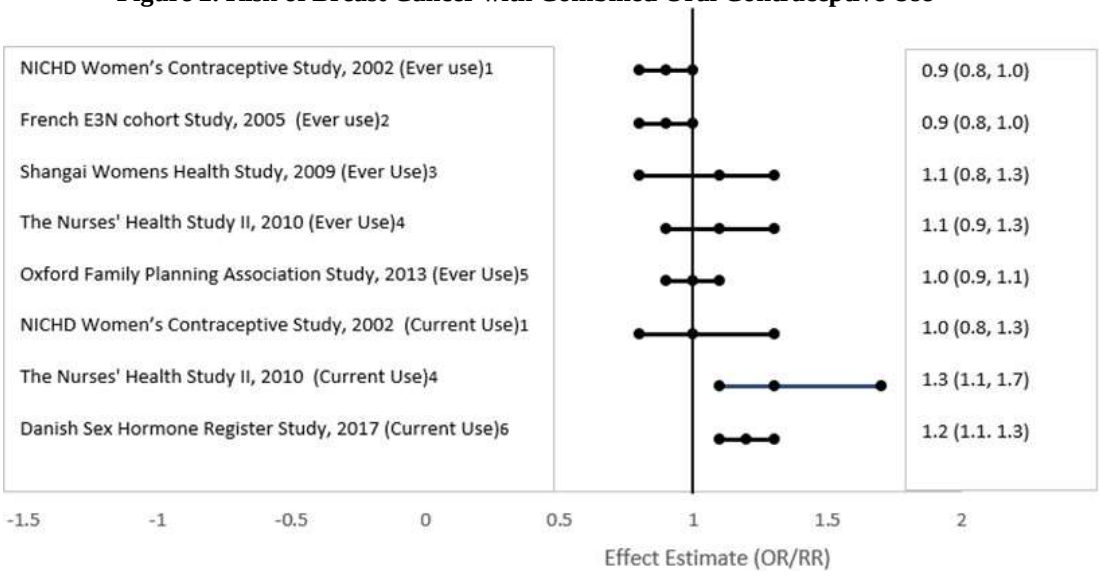
4.8 Undesirable effects Summary of the safety profilePost

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 2).

Three studies compared breast cancer risk between current or recent COC users (<6 months since last use) and never users of COCs (Figure 2). One of these studies reported noassociation 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 foundan 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 2. Risk of Breast Cancer with Combined Oral Contraceptive Use



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

The following serious adverse reactions with the use of COCs are discussed elsewhere in the section 4.4:

- Serious cardiovascular adverse events
- Vascular events
- Liver disease
- Hypertension
- Gallbladder disease
- Carbohydrate and lipid effects
- Headache
- Carcinoma of the cervix

Adverse reactions reported by COC users are:

- Bleeding irregularities and amenorrhea
- Mood changes, including depression
- Melasma/chloasma which may persist
- Edema/fluid retention
- Diminution in lactation when given immediately postpartum

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: Breast tenderness, pain, enlargement, secretion; Nausea, vomiting and gastrointestinal symptoms (such as abdominal pain, cramps and bloating); Change in menstrual flow; Temporary infertility after discontinuation of treatment; Changein weight or appetite (increase or decrease); Change in cervical erosion and secretion;Cholestatic jaundice; Rash (allergic); Vaginitis, including candidiasis; Change in corneal curvature (steepening); Intolerance to contact lenses; Mesenteric thrombosis; Decrease in serum folate levels; Exacerbation of systemic lupus erythematosus; Exacerbation of porphyria; Exacerbation of chorea; Aggravation of varicose veins; Anaphylactic/anaphylactoid reactions, including urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms.

The following adverse reactions have been reported in users of oral contraceptives, and the association has been neither confirmed nor refuted: Congenital anomalies; Premenstrual syndrome; Cataracts; Optic neuritis, which may lead to partial or complete loss of vision; Cystitis-like syndrome; Nervousness; Dizziness; Hirsutism; Loss of scalp hair; Erythema multiforme; Erythema nodosum; Hemorrhagic eruption; Impaired renal function; Hemolytic uremic syndrome; Budd-Chiari syndrome; Acne; Changes in libido; Colitis; Sickle-celldisease; Cerebral-vascular disease with mitral valve prolapse; Lupus-like syndromes; Pancreatitis; Dysmenorrhea.

4.9 Overdose

There have been no reports of serious adverse outcomes from overdose of COCs, including ingestion by children. Overdose may cause uterine bleeding in females and nausea.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

5.2 Pharmacokinetic properties

Absorption

No specific investigation of the absolute bioavailability of Levonorgestrel and Ethinyl Estradiol tablets in humans has been conducted. However, literature indicates that Levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability nearly 100%) and is not subject to first-pass metabolism. Ethinyl Estradiol is rapidly and almost completely absorbed from the gastrointestinal tract but, due to first-pass metabolism in gut mucosa and liver, the bioavailability of Ethinyl Estradiol is approximately 43%.

Table 5: Mean ± SD Pharmacokinetic Parameters Following A Single Dose Administration of Two Tablets of Levonorgestrel and Ethinyl Estradiol Tablets in Healthy Female Subjects Under Fasting Conditions

Analyte	AUCt (mean ± SD)	Cmax (mean ± SD)	Tmax (mean ± SD)	T1/2 (mean ± SD)
Levonorgestrel	60.8 ± 25.6 ng*hr/mL	5.6 ± 1.5 ng/mL	1.4 ± 0.3 hours	29.8 ± 8.3 hours
Ethinyl Estradiol	1307 ± 361 pg*hr/mL	145 ± 45 pg/mL	1.6 ± 0.5 hours	15.4 ± 3.2 hours

The effect of food on the rate and the extent of Levonorgestrel and Ethinyl Estradiol absorption following oral administration of Levonorgestrel and Ethinyl Estradiol tablets has not been evaluated.

Distribution

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

Metabolism

Following absorption, Levonorgestrel is conjugated at the 17β-OH position to form sulfate and to a lesser extent, glucuronide conjugates in plasma. Significant amounts of conjugated and unconjugated 3α,5β-tetrahydrolevonorgestrel are also present in plasma, along with much smaller amounts of 3α,5α-tetrahydrolevonorgestrel and 16β-hydroxylevonorgestrel. Levonorgestrel and its phase I metabolites are excreted primarily as glucuronide conjugates. Metabolic clearance rates may differ among individuals by several-fold, and this may accountin part for the wide variation observed in Levonorgestrel concentrations among users.

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

Excretion

About 45% of Levonorgestrel and its metabolites are excreted in the urine and about 32% are excreted in feces, mostly as glucuronide conjugates. The terminal elimination half-life for Levonorgestrel after a single dose of Levonorgestrel and Ethinyl Estradiol tablets about 30 hours.

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

Special Populations

Race

No formal studies on the effect of race on the pharmacokinetics of Levonorgestrel and Ethinyl Estradiol tablets were conducted.

Hepatic Insufficiency

No formal studies have been conducted to evaluate the effect of hepatic disease on the pharmacokinetics of Levonorgestrel and Ethinyl Estradiol tablets. However, steroidhormones may be poorly metabolized in patients with impaired liver function.

Renal Insufficiency

No formal studies have been conducted to evaluate the effect of renal disease on the pharmacokinetics of Levonorgestrel and Ethinyl Estradiol tablets.

5.3 Preclinical safety data

Preclinical data reveal no special risks for humans based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. However, it should be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Levonorgestrel and Ethinyl Estradiol Tablets USP, (0.15mg/0.03mg)

- Lactose Monohydrate (Pharmatose® 200M)
- Microcrystalline cellulose (Avicel pH 101)
- FD&C yellow #6 / Sunset Yellow FCF Lake
- Povidone (Plasdone K-29/32)
- Purified Water
- Microcrystalline cellulose

Ferrous Fumarate Tablets 75mg

- Microcrystalline Cellulose
- Pregelatinized starch
- Crospovidone
- Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Carton pack of 3 x 28 Tablets. Each Triple Laminated Aluminium pouch contains onePVC/PVDC -Alu Blister pack 28’s (21 Active + 7 Ferrous Fumarate Tablets).

6.6 Special precautions for disposal of a used medicinal product or waste materialsderived from such medicinal product and other handling of the product

No special requirements.

7. MARKETING AUTHORISATION HOLDER

NAARI PTE LIMITEDSINGAPORE

8. MARKETING AUTHORISATION NUMBER

Not Applicable

9. DATE OF FIRST AUTHORIZATION NUMBER(S)

Not applicable

10. DATE OF REVISION OF THE TEXT

31.01.2022