HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TAYSOFY safely and effectively. See full prescribing information for TAYSOFY.

TAYSOFY™ (norethindrone acetate and ethinyl estradiol capsules and ferrous fumarate capsules), for oral use

Initial U.S. Approval: 1968

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See Full Prescribing Information for complete boxed warning.

- **Women over 35 years old who smoke should not use TAYSOFY. (4)**
- **Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. (4)**

----------INDICATIONS AND USAGE----------

- TAYSOFY is an estrogen/progestin COC indicated for use by women to prevent pregnancy (1)
- The efficacy of TAYSOFY in women with a body mass index (BMI) of > 35 kg/m^2 has not been evaluated (1, 8.8)

----------DOSAGE AND ADMINISTRATION----------

- Take one capsule by mouth at the same time every day (2.1)
- Take capsules in the order directed on the blister pack (2.1)
- Capsules may be administered without regard to meals (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

TAYSOFY consists of 28 soft gelatin capsules in the following order (3):

- 24 pink capsules (active), each containing 1 mg norethindrone acetate, USP and 20 mcg ethinyl estradiol, USP
- 4 maroon capsules (non-hormonal placebo) each containing 75 mg ferrous fumarate, USP which does not serve any therapeutic purpose

----------CONTRAINDICATIONS----------

- A high risk of arterial or venous thrombotic diseases (4)
- Liver tumors or liver disease (4)
- Undiagnosed abnormal uterine bleeding (4)
- Pregnancy (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Co-administration with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (4)

----------WARNINGS AND PRECAUTIONS----------

- Vascular risks: Stop TAYSOFY if a thrombotic event occurs. Stop at least 4 weeks before through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding (5.1)
- Liver disease: Discontinue if jaundice occurs (5.2)
- High blood pressure: Do not prescribe TAYSOFY for women with uncontrolled hypertension or hypertension with vascular disease (5.4)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking TAYSOFY. Consider an alternative contraceptive method for women with uncontrolled dyslipidemia (5.6)
- Headache: Evaluate significant change in headaches and discontinue TAYSOFY if indicated (7)
- Uterine bleeding: Evaluate irregular bleeding or amenorrhea (5.8)

----------ADVERSE REACTIONS----------

The most common adverse reactions in clinical trials (≥ 2%) are headache, vaginal candidiasis, nausea, menstrual cramps, breast tenderness, bacterial vaginitis, abnormal cervical smear, acne, mood swings, and weight gain (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up method or alternative method of contraception when enzyme inducers are used with COCs (7.1)

----------USE IN SPECIFIC POPULATIONS----------

Nursing mothers: Not recommended; can decrease milk production (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 05/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed

FULL PRESCRIBING INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke *[see Contraindications (4)]*.

1 INDICATIONS AND USAGE

TAYSOFY is indicated for use by females of reproductive age to prevent pregnancy *[see Clinical Studies (14)]*.

The efficacy of TAYSOFY in women with a body mass index (BMI) of more than 35 kg/m^2 has not been evaluated.

2 DOSAGE AND ADMINISTRATION

2.1 How to Take TAYSOFY

To achieve maximum contraceptive effectiveness, TAYSOFY must be taken exactly as directed. Instruct patients to take one capsule by mouth at the same time every day. Capsules must be taken in the order directed on the blister pack. Capsules should not be skipped or taken at intervals exceeding 24 hours. For patient instructions for missed pills, see *FDA-approved patient labeling*. TAYSOFY may be administered without regard to meals *[see Clinical Pharmacology (12.3)]*.

2.2 How to Start TAYSOFY

Instruct the patient to begin taking TAYSOFY either on the first day of her menstrual period (Day 1 Start) or on the first Sunday after the onset of her menstrual period (Sunday Start).

Day 1 Start
During the first cycle of TAYSOFY use, instruct the patient to take one pink capsule daily, beginning on Day one (1) of her menstrual cycle (the first day of menstruation is Day one). She should take one pink capsule daily for 24 consecutive days, followed by one maroon capsule daily on days 25 through 28. TAYSOFY should be taken in the order directed on the package at the same time each day. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 7 days if she starts taking TAYSOFY on a day other than the first day of her menstrual cycle. The possibility of ovulation and conception prior to initiation of medication should be considered.

Sunday Start
During the first cycle of TAYSOFY use, instruct the patient to take one pink capsule daily, beginning on the first Sunday after the onset of her menstrual period. She should take one pink capsules capsule daily for 24 consecutive days, followed by one maroon capsule daily on days 25 through 28. TAYSOFY should be taken in the order directed on the package at the same time each day. TAYSOFY should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

The patient should begin her next and all subsequent 28-day regimens of TAYSOFY on the same day of the week that she began her first regimen, following the same schedule. She should begin taking her pink capsules on the next day after ingestion of the last maroon capsule, regardless of whether or not a menstrual period has occurred or is still in progress. Anytime a subsequent cycle of TAYSOFY is started later than the day following administration of the last maroon capsule, the patient should use another method of contraception until she has taken a pink capsule daily for 7 consecutive days.

For postpartum women who do not breastfeed or after a second trimester abortion, start TAYSOFY no earlier than 4 weeks postpartum due to the increased risk of thromboembolism. If the patient starts TAYSOFY postpartum and has not yet had a period, evaluate for possible pregnancy, and instruct her to use an additional method of contraception until she has taken TAYSOFY for 7 consecutive days.

TAYSOFY may be initiated immediately after a first-trimester abortion or miscarriage; if the patient starts TAYSOFY immediately, additional contraceptive measures are not needed.

2.3 Switching from another Hormonal Method of Contraception

If the patient is switching from a combination hormonal method such as:
- Another pill
- Vaginal ring
- Patch

- Instruct her to take the first pink capsule on the day she would have taken her next COC pill. She should not continue taking the tablet from her previous birth control pack, and should not skip any days between packs. If she does not have a withdrawal bleed, rule out pregnancy before starting TAYSOFY.
- If she previously used a vaginal ring or transdermal patch, she should start using TAYSOFY on the day she would have resumed the previous product.

If the patient is switching from a progestin-only method such as a:
- Progestin-only pill
- Implant
- Intrauterine system
- Injection

- She may switch any day from a progestin-only pill; instruct her to take the first pink capsule on the day she would have taken her next progestin-only pill. She should use a non-hormonal method of contraception for 7 consecutive days.
- If switching from an implant or injection, start the first pink capsule on the day her next injection would have been due or on the day of removal of her implant.
- If switching from an IUD, depending on the timing of removal, back-up contraception may be needed.

2.4 Advice in Case of Gastrointestinal Disturbances

If the patient vomits or has diarrhea (within 3 to 4 hours after she takes a pink capsule), she should follow the instructions in the "What to Do if You Miss Capsules" section *[see FDA-approved patient labeling]*.

3 DOSAGE FORMS AND STRENGTHS

TAYSOFY is available in blister packs.

Each blister pack contains 28 soft gelatin capsules in the following order:
- 24 oval, opaque, pale pink (active) soft gelatin capsules, printed with "A3" and each containing 1 mg norethindrone acetate, USP and 20 mcg ethinyl estradiol, USP.
- 4 oval, opaque, maroon, (non-hormonal placebo) soft gelatin capsules, printed with "A9" and each containing 75 mg ferrous fumarate, USP. The ferrous fumarate capsules do not serve any therapeutic purpose.

4 CONTRAINDICATIONS

Do not prescribe TAYSOFY to women 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 *[see Boxed Warning* and *Warnings and Precautions (5.1)]*
  - Have deep vein thrombosis or pulmonary embolism, now or in the past *[see Warnings and Precautions (5.1)]*
  - Have cerebrovascular disease *[see Warnings and Precautions (5.1)]*
  - Have coronary artery disease *[see Warnings and Precautions (5.1)]*
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) *[see Warnings and Precautions (5.1)]*
  - Have inherited or acquired hypercoagulopathies *[see Warnings and Precautions (5.1)]*
  - Have uncontrolled hypertension *[see Warnings and Precautions (5.4)]*
  - Have diabetes mellitus with vascular disease *[see Warnings and Precautions (5.6)]*
  - Have headaches with focal neurological symptoms or have migraine headaches with aura
    - Women over age 35 with any migraine headaches *[see Warnings and Precautions (5.7)]*
- Liver tumors, benign or malignant, or liver disease *[see Warnings and Precautions (5.2)]*

- Undiagnosed abnormal uterine bleeding *[see Warnings and Precautions (5.8)]*
- Pregnancy, because there is no reason to use COCs during pregnancy *[see Warnings and Precautions (5.9)* and *Use in Specific Populations (8.1)]*
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past *[see Warnings and Precautions (5.11)]*
- Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations *[see Warnings and Precautions (5.3)]*

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

Stop TAYSOFY if an arterial or deep venous thrombotic event (VTE) occurs. Stop TAYSOFY if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.

If feasible, stop TAYSOFY at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE.

Start TAYSOFY no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum VTE decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

The use of COCs increases the risk of VTE. However, pregnancy increases the risk of VTE as much or more than the use of COCs. The risk of VTE in women using COCs is 3 to 9 per 10,000 woman-years. The risk of VTE is highest during the first year of use of a COC. The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued.

Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest in older (> 35 years of age), hypertensive women who also smoke. COCs also increase the risk for stroke in women with underlying risk factors.

Use COCs with caution in women with cardiovascular disease risk factors.

5.2 Liver Disease

Impaired Liver Function
Do not use TAYSOFY in women with acute viral hepatitis or severe (decompensated) cirrhosis of liver *[see Contraindications (4)]*. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded. Discontinue TAYSOFY if jaundice develops.

Liver Tumors
TAYSOFY is contraindicated in women with benign and malignant liver tumors *[see Contraindications (4)]*. Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases per 100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

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

5.3 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 TAYSOFY prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir *[see Contraindications (4)]*. TAYSOFY can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

5.4 High Blood Pressure

TAYSOFY is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease *[see Contraindications (4)]*. For women with well-controlled hypertension, monitor blood pressure and stop TAYSOFY if blood pressure rises significantly.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women with extended duration of use. The incidence of hypertension increases with increasing concentrations of progestin.

5.5 Gallbladder Disease

Studies suggest a small increased relative 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. Women with a history of pregnancy-related cholestasis may be at an increased risk for COC-related cholestasis.

5.6 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who are taking TAYSOFY. COCs may decrease glucose tolerance in a dose-related fashion.

Consider alternative contraception for women with uncontrolled dyslipidemias. A small proportion of women will have adverse lipid changes while on COCs.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

5.7 Headache

If a woman taking TAYSOFY develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue TAYSOFY if indicated.

Consider discontinuation of TAYSOFY in the case of increased frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) *[see Contraindications (5)]*.

5.8 Bleeding Irregularities and Amenorrhea

Unscheduled Bleeding and Spotting
Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different COC.

Based on patient diaries from a clinical trial evaluating the safety and efficacy of a 24-day regimen of norethindrone acetate 1 mg/ethinyl estradiol 0.020 mg tablets, 24% to 35% of women experienced unscheduled bleeding per cycle. A total of 10 subjects out of 743 (1.3%) discontinued due to bleeding or spotting.

Amenorrhea and Oligomenorrhea
Women who are not pregnant and use TAYSOFY may experience amenorrhea. In the clinical trial with a 24-day regimen of norethindrone acetate 1 mg/ethinyl estradiol 0.020 mg tablets, 22% to 36% of the women using norethindrone acetate 1 mg/ethinyl estradiol 0.020 mg tablets experienced amenorrhea in at least one of 6 cycles of use. Some women may experience post-pill amenorrhea or oligomenorrhea, especially when such a condition was preexistent.

If scheduled (withdrawal) bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active capsules 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 take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

5.9 COC Use before or during Early Pregnancy

Extensive epidemiologic studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when oral contraceptives are taken inadvertently during early pregnancy. Discontinue TAYSOFY if pregnancy is confirmed.

Administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy *[see Use in Specific Populations (8.1)]*.

5.10 Depression

Carefully observe women with a history of depression and discontinue TAYSOFY if depression recurs to a serious degree.

5.11 Carcinoma of the Breast and Cervix

TAYSOFY is contraindicated in women who currently have or have had breast cancer because breast cancer may be hormonally-sensitive *[see Contraindications (4)]*.

There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

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

5.12 Effect on Binding Globulins

The estrogen component of COCs 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.

5.13 Monitoring

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.14 Hereditary Angioedema

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

5.15 Chloasma

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking TAYSOFY.

6 ADVERSE REACTIONS

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

- Serious cardiovascular events and stroke *[see Boxed Warning* and *Warnings and Precautions (5.1)]*
- Vascular events *[see Warnings and Precautions (5.1)]*
- Liver disease *[see Warnings and Precautions (5.2)]*

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data presented in Section 6.1 are from a clinical trial conducted with a 24-day regimen of norethindrone acetate 1 mg/ethinyl estradiol 0.020 mg tablets. TAYSOFY is bioequivalent to these norethindrone acetate/ethinyl estradiol tablets.

Common Adverse Reactions (≥ 2% of all Treated Subjects): The most common adverse reactions reported by at least 2% of the 743 women using norethindrone acetate/ethinyl estradiol tablets were the following, in order of decreasing incidence: headache (6.3%), vaginal candidiasis (6.1%), nausea (4.6%), menstrual cramps (4.4%), breast tenderness (3.4%), bacterial vaginitis (3.1%), abnormal cervical smear (3.1%), acne (2.7%), mood swings (2.2%), and weight gain (2.0%).

Adverse Reactions Leading to Study Discontinuation: Among the 743 women using norethindrone acetate/ethinyl estradiol tablets, 46 women (6.2%) withdrew because of an adverse event. Adverse events occurring in 3 or more subjects leading to discontinuation of treatment were, in decreasing order: abnormal or irregular bleeding (1.3%), nausea (0.8%), menstrual cramps (0.5%), and increased blood pressure (0.4%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of a 24-day regimen of norethindrone acetate 1 mg/ethinyl estradiol 0.020 mg tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or evaluate a causal relationship to drug exposure.

Vascular disorders: thrombosis/embolism (coronary artery, pulmonary, cerebral, deep vein).

Hepatobiliary disorders: cholelithiasis, cholecystitis, hepatic adenoma, hemangioma of liver.

Immune system disorders: hypersensitivity reaction.

Skin and subcutaneous disorders: alopecia, rash (generalized and allergic), pruritus, skin discoloration.

GI disorders: nausea, vomiting, abdominal pain.

Musculoskeletal and connective tissue disorders: myalgia.

Eye disorders: blurred vision, visual impairment, corneal thinning, change in corneal curvature (steepening).

Infections and infestations: fungal infection, vaginal infection.

Investigations: change in weight or appetite (increase or decrease), fatigue, malaise, peripheral edema, blood pressure increased.

Nervous system disorders: headache, dizziness, migraine, loss of consciousness.

Psychiatric disorders: mood swings, depression, insomnia, anxiety, suicidal ideation, panic attack, changes in libido.

Renal and urinary disorders: cystitis-like syndrome.

Reproductive system and breast disorders: breast changes (tenderness, pain, enlargement, and secretion), premenstrual syndrome, dysmenorrhea.

Cardiovascular: chest pain, palpitations, tachycardia, myocardial infarction.

7 DRUG INTERACTIONS

Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

7.1 Effects of Other Drugs on Combined Oral Contraceptives

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate and products containing St. John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma concentrations of COCs: Co-administration of atorvastatin and certain COCs containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol concentrations, possibly by

inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone concentrations.

Human immunodeficiency virus (HIV)/ Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentrations of estrogen and progestin have been noted in some cases of co-administration with HIV/HCV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

7.2 Effects of Combined Oral Contraceptives on Other Drugs

COCs containing ethinyl estradiol may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentration of thyroid-binding globulin increases with use of COCs.

7.3 Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation

Do not co-administer TAYSOFY with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations *[see Warnings and Precautions (5.3)]*.

7.4 Interference with Laboratory Tests

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

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

8.3 Nursing Mothers

When possible, advise the nursing mother to use other forms of contraception until she has weaned her child. COCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

8.4 Pediatric Use

Safety and efficacy of TAYSOFY have been established in women of reproductive age. Efficacy is expected to be the same in postpubertal adolescents under the age of 18 years as for users 18 years and older. Use of this product before menarche is not indicated.

8.5 Geriatric Use

TAYSOFY has not been studied in postmenopausal women and is not indicated in this population.

8.6 Renal Impairment

The pharmacokinetics of TAYSOFY has not been studied in subjects with renal impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

The pharmacokinetics of TAYSOFY has not been studied in subjects with hepatic impairment. However, steroid hormones may be poorly metabolized in patients with hepatic impairment. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded *[see Contraindications (4)* and *Warnings and Precautions (5.2)]*.

8.8 Body Mass Index

The safety and efficacy of TAYSOFY in women with a body mass index (BMI) > 35 kg/m^2 has not been evaluated *[see Clinical Studies (14)]*.

10 OVERDOSAGE

There have been no reports of serious ill effects from overdose of oral contraceptives, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

11 DESCRIPTION

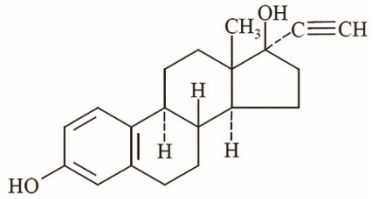
Norethindrone acetate and ethinyl estradiol capsules and ferrous fumarate capsules contain norethindrone acetate USP, a progestin, and ethinyl estradiol USP, an estrogen. TAYSOFY provides an oral contraceptive regimen consisting of 24 pink active soft gelatin capsules that contain the active ingredients, followed by 4 maroon non-hormonal placebo soft gelatin capsules as specified below:

- 24 oval, opaque, pale pink soft gelatin capsules each containing 1 mg norethindrone acetate, USP and 20 mcg ethinyl estradiol, USP.
- 4 oval, opaque, maroon, soft gelatin capsules each containing 75 mg ferrous fumarate, USP

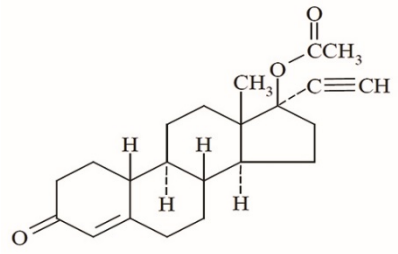
Each pink active capsule also contains the following inactive ingredients: sesame oil, linoleoyl polyoxylglycerides, DL-α-tocopherol, dehydrated alcohol, gelatin, sorbitol sorbitan solution, glycerin, FD&C Red #40, titanium dioxide and purified water.

Each maroon non-hormonal placebo capsule contains ferrous fumarate USP, soybean oil, yellow beeswax, soy lecithin gelatin, sorbitol sorbitan solution, glycerin, FD&C Blue #1, FD&C Red #40, titanium dioxide and purified water. The ferrous fumarate capsules do not serve any therapeutic purpose.

The chemical name of ethinyl estradiol, USP is [19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-]. The empirical formula of ethinyl estradiol, USP is $C_{20}H_{24}O_2$ and the structural formula is:



The chemical name of norethindrone acetate, USP is [19-Norpregn-4-en-20-yn-3-one, 17-(acetyloxy)-, (17α)-]. The empirical formula of norethindrone acetate, USP is $C_{22}H_{28}O_3$ and the structural formula is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit

sperm penetration and endometrial changes that reduce the likelihood of implantation.

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with TAYSOFY.

12.3 Pharmacokinetics

Absorption
In a single-dose, crossover clinical study conducted in 39 healthy, non-smoking premenopausal women under fasting condition, NA/EE capsules were bioequivalent to norethindrone acetate 1 mg/ethinyl estradiol 0.020 mg tablets (24-day regimen tablets) based on the exposure (AUC) and peak concentration (C_{max}) of norethindrone and ethinyl estradiol.

Norethindrone acetate appears to be completely and rapidly deacetylated to norethindrone after oral administration, because the disposition of norethindrone acetate is indistinguishable from that of orally administered norethindrone. Norethindrone acetate and ethinyl estradiol are rapidly absorbed from norethindrone acetate/ethinyl estradiol tablets, with maximum plasma concentrations of norethindrone and ethinyl estradiol occurring 1 to 4 hours post-dose. Both are subject to first-pass metabolism after oral dosing, resulting in an absolute bioavailability of approximately 64% for norethindrone and 43% for ethinyl estradiol.

The plasma norethindrone and ethinyl estradiol pharmacokinetics following single- and multiple-dose administrations of norethindrone acetate/ethinyl estradiol tablets in 17 healthy female volunteers are provided in Figures 1 and 2, and Table 1.

Following multiple-dose administration of norethindrone acetate/ethinyl estradiol tablets, mean maximum concentrations of norethindrone and ethinyl estradiol were increased by 95% and 27%, respectively, as compared to single-dose administration. Mean norethindrone and ethinyl estradiol exposures (AUC values) were increased by 164% and 51% respectively, as compared to single-dose administration of norethindrone acetate/ethinyl estradiol tablets.

Steady-state with respect to norethindrone was reached by Day 17 and steady-state with respect to ethinyl estradiol was reached by Day 13.

Mean SHBG concentrations were increased by 150% from baseline (57.5 nmol/L) to 144 nmol/L at steady-state.

Figure 1. Mean Plasma Norethindrone Concentration-Time Profiles Following Single- and Multiple-Dose Oral Administration of Norethindrone Acetate/Ethinyl Estradiol Tablets to Healthy Female Volunteers under Fasting Condition (n = 17)

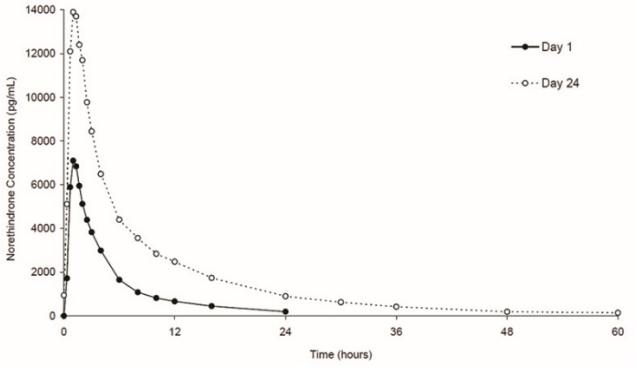


Figure 2. Mean Plasma Ethinyl Estradiol Concentration-Time Profiles Following Single- and Multiple-Dose Oral Administration of Norethindrone Acetate/Ethinyl Estradiol Tablets to Healthy Female Volunteers Under Fasting Condition (n = 17)

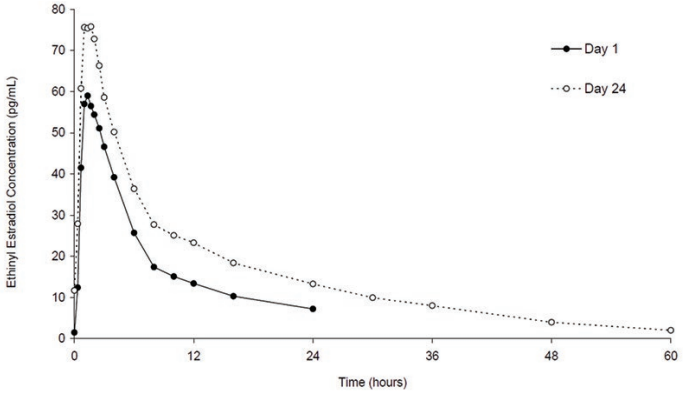


Table 1. Summary of Norethindrone (NE) and Ethinyl Estradiol (EE) Pharmacokinetics Following Single- and Multiple-Dose Oral Administration of Norethindrone Acetate/Ethinyl Estradiol Tablets to Healthy Female Volunteers Under Fasting Condition (n = 17)

Regimen	Analyte	Arithmetic Mean[a] (% CV) by Pharmacokinetic Parameter					
		C_{max} (pg/mL)	t_{max} (hr)	$AUC_{(0-24)}$ (pg/mL•h)	C_{min} (pg/mL)	$t_{½}$ (hr)	C_{avg} (pg/mL)
Day 1 (Single Dose)	NE	8,420 (31)	1.0 (0.7 to 4.0)	33,390 (40)	--	--	--
	EE	64.5 (27)	1.3 (0.7 to 4.0)	465.4 (26)	--	--	--
	SHBG	--	--	--	57.5 (37)[b]	--	--
Day 24 (Multiple Dose)	NE	16,400 (26)	1.3 (0.7 to 4.0)	88,160 (30)	880 (51)	8.4	3,670 (30)
	EE	81.9 (24)	1.7 (1.0 to 2.0)	701.3 (28)	11.4 (43)	14.5	29.2 (28)
	SHBG	--	--	--	144 (24)	--	--

C_{max} = Maximum plasma concentration
t_{max} = Time of C_{max}
C_{min} = minimum plasma concentration at steady-state
$AUC_{(0-24)}$ = Area under plasma concentration versus time curve from 0 to 24 hours
$t_{½}$ = Apparent first-order terminal elimination half-life
C_{avg} = Average plasma concentration = $AUC_{(0-24)/24}$
% CV = Coefficient of Variation (%)
SHBG = Sex Hormone Binding Globulin (nmol/L)
[a]The harmonic mean (0.693/mean apparent elimination rate constant) is reported for $t_{½}$, and the median (range) is reported for t_{max}.
[b]The SHBG concentration reported here is the pre-dose concentration.

Food Effect
TAYSOFY may be administered without regard to meals.

A single-dose administration of NA/EE capsules with food in 38 healthy, non-smoking premenopausal women decreased the maximum concentration of norethindrone and ethinyl estradiol by 38% and 33%, respectively. Food intake did not affect the extent of ethinyl estradiol absorption, but increased the extent of norethindrone absorption by 19%.

Distribution
Volume of distribution of norethindrone and ethinyl estradiol ranges from 2 to 4 L/kg. Plasma protein binding of both steroids is extensive (>95%); norethindrone binds to both albumin and SHBG, whereas ethinyl estradiol binds only to albumin. Although ethinyl estradiol does not bind to SHBG, it induces SHBG synthesis.

Metabolism
Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites.

Ethinyl estradiol is also extensively metabolized, both by oxidation and by conjugation with sulfate and glucuronide. Sulfates are the major circulating conjugates of ethinyl estradiol and glucuronides predominate in urine. The primary oxidative metabolite is 2-hydroxy ethinyl estradiol, formed by the CYP3A4 isoform of cytochrome P450. Part of the first-pass metabolism of ethinyl estradiol is believed to occur in gastrointestinal mucosa. Ethinyl estradiol may undergo enterohepatic circulation.

Excretion
Norethindrone and ethinyl estradiol are excreted in both urine and feces, primarily as metabolites. Plasma clearance values for norethindrone and ethinyl estradiol are similar (approximately 0.4 L/hr/kg). Steady-state elimination half-lives of norethindrone and ethinyl estradiol following administration of norethindrone acetate/ethinyl estradiol tablets are approximately 8 hours and 14 hours, respectively.

Drug Interactions

No drug-drug interaction studies were conducted with TAYSOFY.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[See Warnings and Precautions (5.2, 5.11) and *Use in Specific Populations (8.1)].*

14 CLINICAL STUDIES

The data presented in Section 14 are from a clinical trial conducted with a 24-day regimen of norethindrone acetate 1 mg/ethinyl estradiol 0.020 mg tablets. TAYSOFY is bioequivalent to these norethindrone acetate/ethinyl estradiol tablets.

In a clinical study, 743 women 18 to 45 years of age were studied to assess the efficacy of norethindrone acetate/ethinyl estradiol tablets, for up to six 28-day cycles providing a total of 3,823 treatment-cycles of exposure. The racial demographic of all enrolled women was: 70% Caucasian, 16% African-American, 10% Hispanic, 2% Asian and 2% Other. Women with body mass index (BMI) greater than 35 mg/m^2 were excluded from the study. The weight range for those women treated was 90 to 260 pounds, with a mean weight of 147 pounds. Among the women in the study, about 40% had not used hormonal contraception immediately prior to enrolling in this study.

A total of 583 women completed 6 cycles of treatment. There were a total of 5 on-treatment pregnancies in 3,565 treatment cycles during which no backup contraception was used. The Pearl Index for norethindrone acetate/ethinyl estradiol tablets was 1.82 (95% confidence interval 0.59 to 4.25).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

TAYSOFY (norethindrone acetate and ethinyl estradiol capsules, 1 mg/20 mcg and ferrous fumarate capsules, 75 mg) is available in blister cards (dispensers) containing 28 soft gelatin capsules:

Each blister card contains 28 capsules in the following order:
- 24 oval, opaque, pale pink (active) soft gelatin capsules, printed with ‘A3’ and each containing 1 mg norethindrone acetate, USP and 20 mcg ethinyl estradiol, USP.
- 4 oval, opaque, maroon, (non-hormonal placebo) soft gelatin capsules, printed with “A9” and each containing 75 mg ferrous fumarate, USP. The ferrous fumarate capsules do not serve any therapeutic purpose.

Each blister card is packed in a carton (NDC 65162-558-58).

Cartons of 5 blister cards packed individually in 5 cartons are provided for dispensing (NDC 65162-558-15).
5 cartons - each carton contains 1 blister card (28): NDC 65162-558-58

16.2 Storage Conditions

Store at 20° to 25º C (68° to 77º F); excursions permitted between 15° to 30º C (59° to 86º F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Counsel patients on the following information:

- Cigarette smoking increases the risk of serious cardiovascular events from COC use, and women who are over 35 years old and smoke should not use COCs.
- Increased risk of VTE compared to non-users of COCs is greatest after initially starting a COC or restarting (following a 4-week or greater pill-free interval) the same or a different COC.
- TAYSOFY does not protect against HIV infection (AIDS) and other sexually transmitted infections.
- The Warnings and Precautions associated with COCs.
- TAYSOFY is not to be used during pregnancy; if pregnancy occurs during use of TAYSOFY, instruct the patient to stop further intake.
- Take one capsule daily by mouth at the same time every day. Instruct patients what to do in the event pills are missed. See “What to Do if You Miss Capsules” section in FDA-approved patient labeling.
- Use a back-up or alternative method of contraception when enzyme inducers are used with TAYSOFY.
- COCs may reduce breast milk production. This is less likely to occur if breastfeeding is well established.
- Women who start COCs postpartum, and who have not yet had a period, should use an additional method of contraception until they have taken a pink capsule for 7 consecutive days.
- Amenorrhea may occur. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles.

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