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

NEXTSTELLIS (drospirenone and estetrol tablets), for oral use
Initial U.S. Approval: 2021

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS
See full prescribing information for complete boxed warning.
- **Females over 35 years old who smoke should not use NEXTSTELLIS (4)**
- **Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. (4)**

----------RECENT MAJOR CHANGES----------
Warnings and Precautions (5.5) 04/2022

----------INDICATIONS AND USAGE----------
NEXTSTELLIS is a combination of drospirenone, a progestin, and estetrol, an estrogen, indicated for use by females of reproductive potential to prevent pregnancy. (1)

Limitations of Use
NEXTSTELLIS may be less effective in females with a BMI ≥ 30 kg/m^2. In females with BMI ≥ 30 kg/m^2, decreasing effectiveness may be associated with increasing BMI (14).

----------DOSAGE AND ADMINISTRATION----------
- Take one tablet by mouth at the same time every day. (2.1)
- Take tablets in the order directed on the blister pack. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
NEXTSTELLIS consists of 28 tablets in the following order (3):
- 24 pink active tablets each containing drospirenone 3 mg and estetrol 14.2 mg
- 4 white inert tablets

----------CONTRAINDICATIONS----------
- A high risk of arterial or venous thrombotic diseases (4)
- Breast cancer or history of breast cancer (4)
- Hepatic adenoma, hepatocellular carcinoma, acute hepatitis or decompensated cirrhosis (4)
- Co-administration with hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (4, 7.1)
- Abnormal uterine bleeding that has an undiagnosed etiology (4)
- Renal impairment (4)
- Adrenal insufficiency (4)

----------WARNINGS AND PRECAUTIONS----------
- Thromboembolic Disorders and Other Vascular Problems: Stop NEXTSTELLIS if a thrombotic or thromboembolic event occurs. Start no earlier than 4 weeks after delivery. Consider all cardiovascular risk factors before initiating in any female, particularly in the presence of multiple risk factors. (5.1)
- Hyperkalemia: Check serum potassium concentration during the first NEXTSTELLIS treatment cycle in females on long-term treatment with medications that may increase serum potassium concentration. (5.2, 7.2)
- Hypertension: Monitor blood pressure periodically and stop use if blood pressure rises significantly. (5.3)
- Migraine: Discontinue if new, recurrent, persistent, or severe migraines occur. (5.4)
- Hormonally-Sensitive Malignancy: Discontinue NEXTSTELLIS if a hormonally-sensitive malignancy is diagnosed. (5.5)
- Liver Disease: Withhold or permanently discontinue for persistent or significant elevation of liver enzymes. (5.6)
- Glucose Tolerance and Hypertriglyceridemia: Monitor glucose in females with prediabetes or diabetes. Consider an alternate contraceptive method for females with hypertriglyceridemia. (5.8)
- Gallbladder Disease and Cholestasis: Consider discontinuing NEXTSTELLIS in females with symptomatic gallbladder or cholestatic disease. (5.9)
- Bleeding Irregularities and Amenorrhea: May cause irregular bleeding or amenorrhea. Evaluate for other causes if symptoms persist. (5.11)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥2%): bleeding irregularities, mood disturbance, headache, breast symptoms, dysmenorrhea, acne, weight increased, and libido decreased (6)

To report SUSPECTED ADVERSE REACTIONS, contact Mayne Pharma at 1-844-825-8500 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
- CYP3A Inducers: May lead to contraceptive failure and/or increase breakthrough bleeding. Avoid concomitant use. If concomitant use is unavoidable, use an alternative or back-up contraceptive method during co-administration and up to 28 days after discontinuation of the CYP3A inducer. (7.1)
- See Full Prescribing Information for additional clinically significant drug interactions (7).

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Discontinue if pregnancy occurs. (8.1)
- Lactation: Advise postpartum females that NEXTSTELLIS can decrease milk production. (8.2)

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

Revised: 04/2022

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 combined hormonal contraceptive (CHC) use. This risk increases with age, particularly in females over 35 years of age, and with the number of cigarettes smoked. For this reason, CHCs, including NEXTSTELLIS, are contraindicated in females who are over 35 years of age and smoke. *[See Contraindications (4) and Warnings and Precautions (5.1)]*

1 INDICATIONS AND USAGE

NEXTSTELLIS is indicated for use by females of reproductive potential to prevent pregnancy.

Limitations of Use

NEXTSTELLIS may be less effective in females with a BMI ≥ 30 kg/m^2. In females with BMI ≥ 30 kg/m^2, decreasing effectiveness may be associated with increasing BMI *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage and Administration

Start NEXTSTELLIS using a Day 1 start. Take one tablet by mouth at the same time every day with or without food.

2.2 Additional Administration Information

To achieve maximum contraceptive effectiveness, Take one tablet every day at about the same time each day. The recommended dosage of NEXTSTELLIS is one tablet daily for 28 consecutive days: one pink active tablet daily during the first 24 days followed by one white inactive tablet daily during the 4 following days (see Table 1).

Table 1 NEXTSTELLIS Administration Instructions

Starting NEXTSTELLIS in females with no current use of hormonal contraception	**Important:** • In females with irregular menstrual cycles, pregnancy testing may be necessary prior to initiation of this product. **Day 1 Start**: • Take the first pink active tablet on the first day of menses. • Take subsequent pink active tablets once daily at the same time each day for a total of 24 days. • Take one white inert tablet daily for 4 days and at the same time of day that active tablets were taken. • Begin each subsequent 28-day pack on the same day of the week as the first cycle pack (i.e., on the day after taking the last tablet) If not starting on the first day of menses, use a non-hormonal contraceptive (e.g. condoms and/or spermicide) as back-up until one active tablet has been taken daily for 7 days in a row.

Switching to NEXTSTELLIS from another contraceptive method	**Start NEXTSTELLIS on the day:**
• Combined Oral Contraceptive (COC)	• When the new pack of the previous COC would have started.
• Transdermal System	• When the next application would have been scheduled.
• Vaginal Insert	• When the next insertion would have been scheduled.
• Injection	• When the next injection would have been scheduled.
• Intrauterine System (IUS)	• After removal.
• Implant	• After removal.
• Progestin-only pill	• After the last tablet was taken.
Starting NEXTSTELLIS after delivery (>20 weeks gestation)	Must not start earlier than 4 weeks after delivery (due to the increased risk of thromboembolism *[see Contraindications (4) and Warnings and Precautions (5.1)]* If menstrual cycles have returned, follow instructions for "Starting NEXTSTELLIS in females with no current use of hormonal contraception". If menstrual cycles have not resumed, consider the possibility of ovulation and pregnancy. If not pregnant, use additional nonhormonal contraception for the first 7 days of NEXTSTELLIS use.
Starting NEXTSTELLIS after Abortion or Miscarriage • **≤14 weeks gestation**	Within the first 7 days of complete first trimester abortion or miscarriage, use additional nonhormonal contraception for the next 7 days. After the first 7 days, follow instructions for "Starting NEXTSTELLIS in females with no current use of hormonal contraception".
• **> 14 weeks but ≤ 20 weeks gestation**	After 4 weeks following second trimester abortion or miscarriage. Consider duration of pregnancy and increased risk of thromboembolism *[see Warnings and Precautions (5.1)]* If menstrual cycles have returned, follow instructions for "Starting NEXTSTELLIS in females with no current use of hormonal contraception." If menstrual cycles have not resumed, consider the possibility of ovulation and pregnancy. If not pregnant, use additional nonhormonal contraception for the first 7 days of NEXTSTELLIS use.

2.3 Missed Doses

Table 2 Instructions for Missed NEXTSTELLLIS Tablets in a Monthly Dosing Regimen

• If one pink active tablet is missed	Take the missed tablet as soon as possible and take the next tablet at the scheduled time, even if two active tablets are taken in one day. Continue taking one tablet a day until the pack is finished.
• If two or more pink active tablets are missed in Week 1 or Week 2	Take one missed tablet as soon as possible and take the tablet for the current day (that means taking two tablets in one day) and discard the other missed tablets. Continue taking one tablet a day until the pack is finished. Use additional non-hormonal contraception as back-up until pink tablets have been taken for 7 consecutive days.
• If two pink active tablets are missed in Week 3	Take one missed tablet as soon as possible and take the tablet for the current day (that means taking two tablets in one day) and discard the other missed tablets. Finish the active tablets and discard the inactive tablets in the pack. Start a new pack of tablets the next day. Use additional non-hormonal contraception as back-up until pink tablets have been taken for 7 consecutive days.
• If one or more white inert tablets are missed	Skip the missed pill days and continue taking one tablet a day until the pack is finished.

2.4 Administration Recommendations after Vomiting or Acute Diarrhea

If vomiting or acute diarrhea occurs within 3 to 4 hours after taking an active tablet, take the new active tablet (scheduled for the next day) as soon as possible. Take the new tablet within 12 hours of the usual time of tablet-taking if possible. If more than two tablets are missed, follow the advice concerning missed tablets, including using backup non-hormonal contraception. For additional recommendations, refer to the table above *[see Dosage and Administration (2.3)].*

3 DOSAGE FORMS AND STRENGTHS

NEXTSTELLIS (drospirenone and estetrol tablets) is available in a blister card, with 28 6-mm round, bi-convex film-coated tablets in the following order:

- 24 pink active tablets containing 3 mg drospirenone and 14.2 mg estetrol embossed with a drop-shaped logo on one side.
- 4 white inert tablets embossed with a drop-shaped logo on one side.

4 CONTRAINDICATIONS

NEXTSTELLIS is contraindicated in females who are known to have or develop the following conditions:

- A history of, increased risk for, or current arterial or venous thrombotic/thromboembolic diseases. Examples include females who are known to:
  - Smoke, if 35 years of age and older *[see Boxed Warning and Warnings and Precautions (5.1)]*

- Have current or history of deep vein thrombosis or pulmonary embolism *[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 or hypertension with vascular disease *[see Warnings and Precautions (5.1)]*
- Have diabetes mellitus with hypertension or end-organ damage; or diabetes mellitus of > 20 years duration *[see Warnings and Precautions (5.9)]*
- Have migraine headaches with aura *[see Warnings and Precautions (5.4)]*

- Current diagnosis of, or history of, breast cancer, which may be hormone-sensitive [see Warnings and Precautions (5.5)]
- Hepatic adenoma, hepatocellular carcinoma, acute hepatitis, or severe (decompensated) cirrhosis *[see Warnings and Precautions (5.6)]*
- 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 (5.7)]*
- Abnormal uterine bleeding that has an undiagnosed etiology *[see Warnings and Precautions (5.5)]*
- Renal Impairment *[see Warnings and Precautions (5.2)]*
- Adrenal insufficiency *[see Warnings and Precautions (5.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

- Stop NEXTSTELLIS if an arterial or venous thrombotic/thromboembolic event occurs.
- Stop NEXTSTELLIS if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions and evaluate for retinal vein thrombosis immediately.
- Discontinue NEXTSTELLIS during prolonged immobilization.
- Start NEXTSTELLIS 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 NEXTSTELLIS, evaluate any past medical history or family history of thrombotic or thromboembolic disorders and consider whether the history suggests an inherited or acquired hypercoagulopathy. NEXTSTELLIS is contraindicated in females with a high risk of arterial or venous thrombotic/thromboembolic diseases *[see Contraindications (4)]*.

Cardiovascular and Cerebrovascular Events

Use of CHCs increases the risk of cardiovascular events and cerebrovascular events, such as myocardial infarction and stroke. The risk is greater among females over age 40, smokers, and females with hypertension, dyslipidemia, diabetes, or obesity. The risk increases with age, particularly in females 35 years of age and older, and with the number of cigarettes smoked. In addition to cigarettes, use of other nicotine-containing products – including cigars, smokeless tobacco, hookah tobacco, e-cigarettes, and nicotine replacement therapy – may also increase the risk of serious cardiovascular events from CHC use.

Venous Thromboembolism

Use of CHCs also increases the risk of venous thromboembolic events (VTEs), such as deep vein thrombosis and pulmonary embolism. The rate of VTE in females using COCs has been estimated to be *3 to 9 cases per 10,000 woman-years* and should be considered in the context of other female of reproductive potential subpopulations who are not taking CHCs *[see Adverse Reactions (6.1)].*

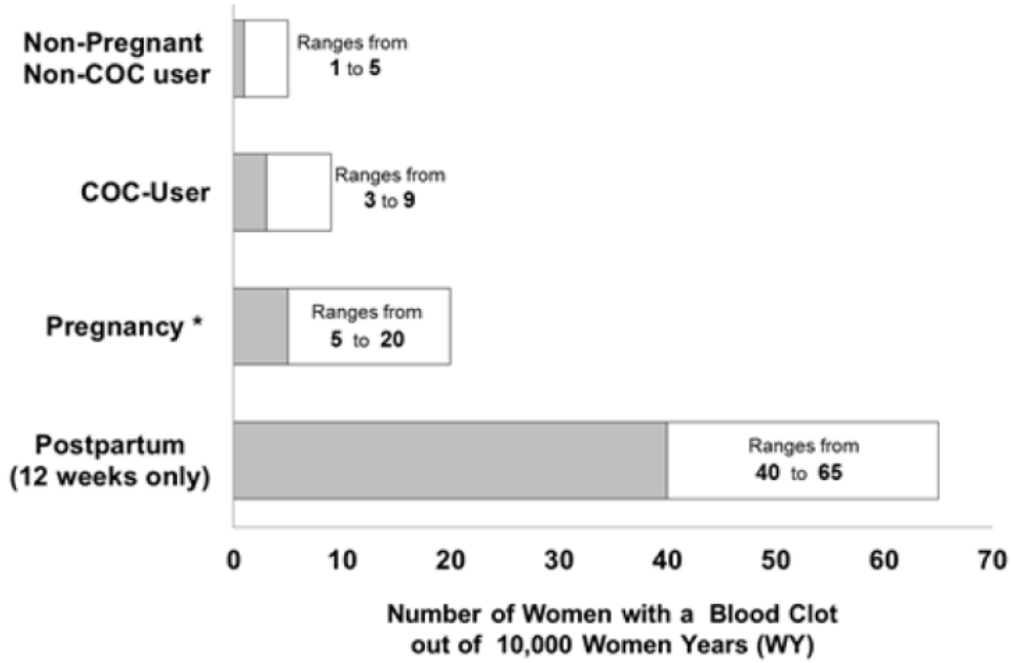
Risk factors for VTEs include smoking, obesity, family history of VTE, and prolonged immobilization in addition to other factors that contraindicate use of CHCs *[see Contraindications (4)]*. The presence of multiple risk factors for VTE may increase the risk synergistically. The risk of VTE is highest during the first year of CHC use and when restarting hormonal contraception after a break of four weeks or longer. The risk of VTE returns to baseline approximately 3 months after CHC use is discontinued.

Postpartum Venous Thromboembolism

The risk of VTE is increased during the first six weeks postpartum compared to the risk in non-pregnant, non-postpartum females. The risk is highest in the first three weeks postpartum, but remains higher than baseline until at least six weeks postpartum. The presence of multiple risk factors for VTE may further increase the risk. Obstetric complications may extend the elevated risk up to 12 weeks postpartum.

Figure 1 shows the risk of developing a VTE for females who are not pregnant and do not use COCs, for females who use COCs, 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



Two prospective studies of NEXTSTELLIS have been conducted, one in Europe/Russia (NCT02817828; C301) and one in North America (NCT02817841; C302) (N=3,632), for the prevention of pregnancy in females 16-50 years of age. There was one reported VTE in the Europe/Russia study *[see Adverse Reactions (6.1)]*.

5.2 Hyperkalemia

NEXTSTELLIS is contraindicated in females with conditions that predispose to hyperkalemia (e.g., renal impairment, hepatic impairment, and adrenal insufficiency). Females receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium concentration should have their serum potassium concentration checked during the first treatment cycle. Monitor serum potassium concentration in females at increased risk for hyperkalemia (i.e., those females who take a strong CYP3A4 inhibitor long-term and concomitantly with NEXTSTELLIS). *[see Drug interactions (7)]*. Monitor females taking NEXTSTELLIS who later develop medical conditions and/or begin medication that put them at an increased risk for hyperkalemia.

NEXTSTELLIS contains drospirenone, a progestin, which has anti-mineralocorticoid activity, including the potential for hyperkalemia in high-risk females, comparable to a 25 mg dose of spironolactone. In two Phase 3 trials of NEXTSTELLIS (N = 3,632) for the prevention of pregnancy in females 16-50 years of age, seven subjects were noted to have hyperkalemia and one subject discontinued due to elevated potassium levels. Most females who developed hyperkalemia in the clinical development studies of NEXTSTELLIS had only mild potassium elevations and/or isolated increases that returned to normal while still on study medication.

5.3 Hypertension

NEXTSTELLIS is contraindicated in females with uncontrolled hypertension or hypertension with vascular disease *[see Contraindications (4)]*. For all females, including those with well-controlled hypertension, monitor blood pressure periodically and stop NEXTSTELLIS if blood pressure rises significantly.

An increase in blood pressure has been reported in females using COCs. This increase is more likely in older females with extended duration of use.

5.4 Migraine

NEXTSTELLIS is contraindicated in females who have migraines with aura *[see Contraindications (4)]*. Discontinue NEXTSTELLIS in females using NEXTSTELLIS who develop new migraines that are recurrent, persistent, or severe. Discontinue NEXTSTELLIS if there is an increased frequency or severity of migraines during CHC use (which may be prodromal of a cerebrovascular event).

Migraines with aura increase the risk for stroke. This stroke risk is further increased in females who have migraines with aura with use of CHCs.

5.5 Malignant Neoplasms

Breast Cancer

NEXTSTELLIS is contraindicated in females who currently have or have had breast cancer because breast cancer may be hormonally sensitive [see Contraindications (4)].

Epidemiology studies have not found a consistent association between use of combined oral contraceptives (COCs) and breast cancer risk. Studies do not show an association between ever (current or past) use of COCs and risk of breast cancer. However, some studies report a small

increase in the risk of breast cancer among current or recent users (<6 months since last use) and current users with longer duration of COC use [see Postmarketing Experience (6.2)].

Cervical Cancer

A causal relationship between the use of CHCs and the development of cervical cancer and intraepithelial neoplasia has not been clearly established. In observational studies, the use of oral hormonal contraceptives in females for five years or more, compared to females who did not use oral hormonal contraceptives, was associated with an increased risk of cervical cancer and intraepithelial neoplasia. In these studies, the use of oral hormonal contraceptives in females for 10 years or more, compared to females who received oral hormonal contraceptives for 5-9 years, was associated with an increased risk of cervical cancer and intraepithelial neoplasia. Limitations in these epidemiologic studies include potential recall bias, differences in sexual behavior, and other factors such as establishing whether there were data on persistent high-risk Human Papilloma Virus (HPV) infection.

5.6 Liver Disease

Elevated Liver Enzymes

NEXTSTELLIS is contraindicated in females with acute hepatitis or severe (decompensated) cirrhosis *[see Contraindications (4)]*. Withhold or permanently discontinue NEXTSTELLIS for persistent or significant elevation of liver enzymes. NEXTSTELLIS can cause elevated liver enzymes.

Liver Tumors

NEXTSTELLIS is contraindicated in females with hepatic adenomas and malignant liver tumors *[see Contraindications (4)]*. CHCs increase the risk of hepatic tumors, particularly hepatic adenomas. Rupture of hepatic adenomas may cause death from abdominal hemorrhage.

5.7 Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

CHCs, such as NEXTSTELLIS, are contraindicated for use with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir (with or without dasabuvir) *[see Contraindications (4)]*. Discontinue NEXTSTELLIS prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir (with or without dasabuvir). NEXTSTELLIS can be restarted approximately 2 weeks following completion of treatment with this hepatitis C combination drug regimen.

During clinical trials with the above-mentioned Hepatitis C combination drug regimen, 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 females using ethinyl estradiol (EE)-containing drugs, such as CHCs. Females using medications containing estrogens other than EE had a rate of ALT elevation similar to those not receiving any estrogens. NEXTSTELLIS contains E4 rather than EE, but as no data are available for co-administration with this Hepatitis C combination drug regimen, caution is warranted.

5.8 Glucose Tolerance and Hypertriglyceridemia

Glucose Tolerance

Carefully monitor females with prediabetes and diabetes who are using NEXSTELLIS. NEXTSTELLIS may decrease glucose tolerance *[see Clinical Pharmacology (12.2)]*.

Hypertriglyceridemia
Consider alternative contraception for females with hypertriglyceridemia. Females with hypertriglyceridemia, or a family history thereof, may have an increase in serum triglyceride concentrations when using NEXSTELLIS, which may increase the risk of pancreatitis.

5.9 Gallbladder Disease and Cholestasis
Consider discontinuing NEXTSTELLIS in females with symptomatic gallbladder disease or cholestatic disease. Studies suggest an increased risk of developing gallbladder disease among CHC users. Use of CHCs may also worsen existing gallbladder disease.

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

5.10 Effect on Binding Globulins
Increase the dosage of thyroid hormone replacement therapy as needed in females taking NEXTSTELLIS *[see Clinical Pharmacology (12.2)].* The estrogen component of NEXTSTELLIS may increase the serum concentrations of thyroxine-binding globulin, sex hormone-binding globulin, and cortisol-binding globulin.

5.11 Bleeding Irregularities and Amenorrhea
Unscheduled Bleeding and Spotting
Females using NEXTSTELLIS may experience unscheduled (breakthrough or intracyclic) bleeding and spotting, especially during the first 4 months of 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.

Unscheduled bleeding was defined as bleeding or spotting that occurred on Day 4 through Day 24 of a 28-day cycle. Based on subject diaries from C302 (US/CA), the proportion of subjects reporting unscheduled bleeding or spotting per 28-day cycle decreased over time: 30.3% at Cycle 1 versus 17.4% at Cycle 12. The mean number of unscheduled bleeding/spotting days per cycle also gradually decreased over time, with a mean of 0.4 (± 1.42) bleeding days at Cycle 1, versus a mean of 0.2 (± 0.98) bleeding days at Cycle 12.

Absence of Scheduled Bleeding
Females who use NEXTSTELLIS may experience absence of scheduled (withdrawal) bleeding, even if they are not pregnant *[See Adverse Reactions (6)]*. The proportion of subjects reporting absence of scheduled bleeding remained constant overall, with on average 15.5% of subjects reporting absence of scheduled bleeding from Cycles 1 through 12.

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 prescribed), consider the possibility of pregnancy at the time of the first missed period and perform appropriate diagnostic measures.

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

5.12 Depression
Monitor females with a history of depression and discontinue NEXTSTELLIS if depression recurs to a serious degree. Data on the association of COCs with onset of depression or exacerbation of existing depression are limited.

5.13 Hereditary Angioedema
Avoid NEXTSTELLIS in females with hereditary angioedema. Exogenous estrogens may induce or exacerbate symptoms of hereditary angioedema.

5.14 Chloasma
Avoid NEXTSTELLIS in females with a history of chloasma gravidarum or increased sensitivity to sun and/or ultraviolet radiation exposure. Chloasma may occur with NEXTSTELLIS use, especially in females with a history of chloasma gravidarum.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions with the use of COCs are discussed elsewhere in labeling:
- Serious cardiovascular events including venous and arterial thromboembolism *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Hyperkalemia *[see Warnings and Precautions (5.2)]*
- Liver disease *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of one drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data provided reflect the experience with the use of NEXTSTELLIS in two large prospective studies, one in Europe/Russia (C301) and one in North America (C302) (N = 3,632) of NEXTSTELLIS for the prevention of pregnancy in females 16-50 years of age. The mean duration of NEXTSTELLIS exposure was 317 and 257 days for the respective studies. The study population was 27 years of age on average, with a mean BMI of 25 kg/m^2. The racial distribution was 83% White; 11% Black; 3% Asian; and 3% Other.

Table 4 Adverse Reactions Occurring in ≥ 2% of Females Receiving NEXTSTELLIS in Studies C301 and C302

Preferred Term (PT)	Participants with Adverse Reaction – US/Canada Phase 3 trial (n [%]) (N = 2073)*	Participants with Adverse Reaction – Two Phase 3 trials (n [%]) (N=3632)**
Any adverse reaction***	1205 (58.1)	2126 (58.5)
Mood disturbance[1]	226 (10.9)	329 (9.1)
Bleeding irregularities[2]	201 (9.7))	393 (10.8)
Breast symptoms[3]	110 (5.3)	197 (5.4)
Headache[4]	100 (4.8)	227 (6.3)
Dysmenorrhea[5]	84 (4.1)	133 (3.7)
Weight increased[6]	68 (3.3)	108 (3.0)

Acne[7]	66 (3.2)	136 (3.7)
Libido decreased/lost[8]	27 (1.3)	72 (2.0)

*Represents the safety population of C302 only (US/Canada).
**Represents the safety population of C301/C302 for DRSP/E4.
***Any adverse reaction equals any adverse event ≥ 2%.

1. Includes PTs: adjustment disorder, affective disorder, agitation, anger, anxiety, depressed mood, depression, depressive symptom, disorientation, emotional disorder, emotional distress, euphoric mood, generalized anxiety disorder, insomnia, irritability, mood altered, mood swings, nervousness, panic attack, panic disorder, performance fear, restlessness, sleep disorder, stress, suicidal ideation, tearfulness
2. Includes PTs: abnormal withdrawal bleeding, amenorrhea, cervix hemorrhage uterine, coital bleeding, dysfunctional uterine bleeding, menometrorrhagia, menorrhagia, menstrual disorder, menstruation irregular, metrorrhagia, oligomenorrhea, polymenorrhea, uterine hemorrhage, vaginal hemorrhage.
3. Includes PTs: anisomastia, breast cyst, breast discoloration, breast discomfort, breast disorder, breast engorgement, breast enlargement, breast mass, breast edema, breast pain, breast swelling, breast tenderness, fibrocystic breast disease, galactorrhea, gynecomastia, mastoptosis, nipple disorder, nipple pain.
4. Includes PTs headache, premenstrual headache, and tension headache.
5. Includes PTs adnexa uteri pain, dysmenorrhea, premenstrual cramps, pelvic discomfort, pelvic pain, uterine spasm.
6. Includes PTs: weight increased, weight fluctuation, body mass index increased, weight loss poor, and obesity.
7. Includes PTs acne and cystic acne.
8. Includes PTs: libido decreased and loss of libido

Adverse Reactions Leading to Study Discontinuation (> 1%)

Of 3,632 females in two clinical studies for prevention of pregnancy in females 16-50 years of age, 9.6% discontinued due to an adverse reaction; the most frequent adverse reaction leading to discontinuation was bleeding irregularity (2.8%). Six subjects (0.17%) discontinued study participation due to new onset of migraine with aura; two subjects (0.05%) discontinued due to severe migraine.

Thromboembolic Disorders and Other Vascular Problems

During studies C301 and C302, one thromboembolic event was reported in a female who had been taking NEXTSTELLIS for 75 days and had normal BMI < 25 kg/m^2.

Depression

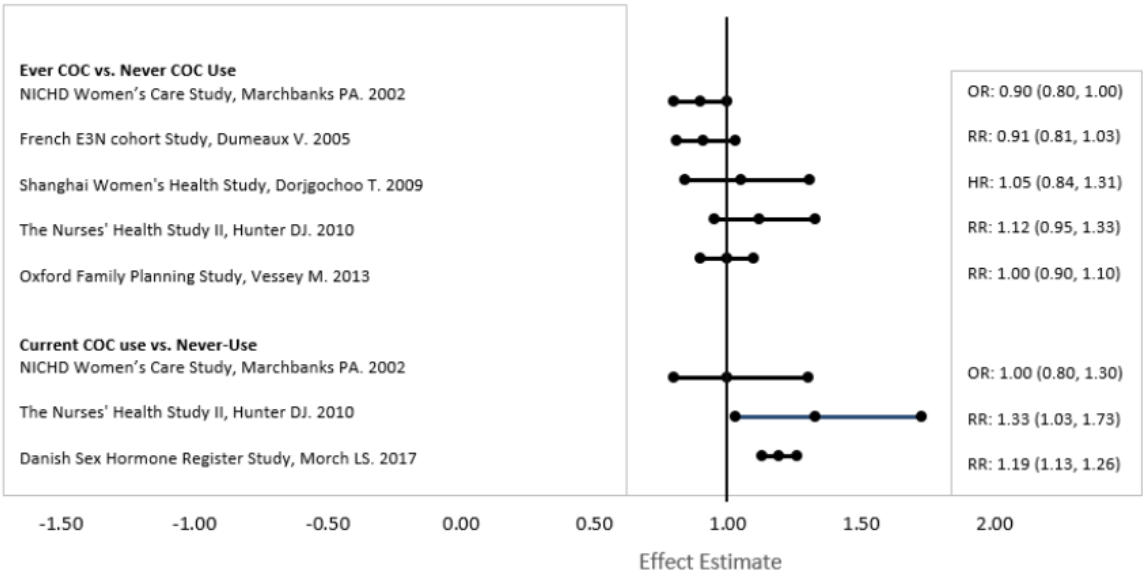
In Study C302 (US/CA), 36 (1.7%) subjects reported depression while using NEXTSTELLIS. Nine (0.3%) subjects had drug withdrawn as a result of symptoms of depression.

6.2 Postmarketing 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 X).

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

Figure 2 Relevant Studies of Risk of Breast Cancer with Combined Oral Contraceptives



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.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on Hormonal Contraceptives

Clinically significant drug interactions with other drugs that affect NEXTSTELLIS are presented in Table 5.

Table 5. Clinically Significant Drug Interactions With Other Drugs that Affect NEXTSTELLIS

CYP3A Inducers		
Clinical Effect	DRSP is a CYP3A4 substrate. Concomitant use with strong CYP3A inducers or certain moderate or weak CYP3A inducers may decrease DRSP exposure *[see Clinical Pharmacology (12.3)]*, which may lead to contraceptive failure.	
Prevention or Management	Strong CYP3A Inducers	Avoid concomitant use. If concomitant use is unavoidable, use an alternative contraceptive method (e.g., intrauterine system) or backup non-hormonal contraceptive method during coadministration and up to 28 days after discontinuation of the strong CYP3A inducer.
	Moderate and Weak CYP3A Inducers	Use an alternative or backup contraceptive method during coadministration and up to 28 days after discontinuation of the CYP3A inducer, unless the Prescribing Information of the specific moderate or weak CYP3A inducer indicates there is no clinically significant interaction with NEXTSTELLIS.
Strong CYP3A Inhibitors		
Clinical Effect	DRSP is a CYP3A4 substrate. Concomitant use with a strong CYP3A inhibitor may increase DRSP exposure *[see Clinical Pharmacology (12.3)]*, which may increase the	

	risk of adverse reactions of NEXTSTELLIS, including hyperglycemia *[see Warnings and Precautions (5.2)]*.
Prevention or Management	Consider monitoring serum potassium concentration in patients who take a strong CYP3A4 inhibitor long-term and concomitantly with NEXTSTELLIS.
Drugs that May Reduce the Absorption of NEXTSTELLIS	
Clinical Effect	Concomitant use with drugs such as bile acid sequestrants may decrease the E4 and DRSP exposure, which may lead to contraceptive failure and/or an increase in breakthrough bleeding.
Prevention or Management	Separate time of administration of NEXTSTELLIS and the concomitant drug. Refer to the concomitant drug's Prescribing Information for additional information.

7.2 Effects of NEXTSTELLIS on Other Drugs

Table 6 includes clinically significant drug interactions with NEXTSTELLIS that affect other drugs.

Table 6. Clinically Significant Drug Interactions of NEXTSTELLIS on Other Drugs

Anti-Diabetic Drugs	
Clinical Effect	Concomitant use of NEXTSTELLIS may reduce the blood glucose lowering effect of anti-diabetic drugs [see Warnings and Precautions (5.8) and Clinical Pharmacology (12.2).
Prevention or Management	Increase frequency of glucose monitoring and increase anti-diabetic drug dosage, as needed, based on glucose levels.
Drugs that may increase serum potassium concentration	
Clinical Effect	There is a potential for an increase in serum potassium concentration in females taking NEXTSTELLIS with other drugs that may increase serum potassium concentration [see Warnings and Precautions (5.2) and Clinical Pharmacology (12.2)].
Prevention or Management	Monitor serum potassium concentration in females at increased risk for hyperkalemia.
Lamotrigine	
Clinical Effect	Concomitant use of NEXTSTELLIS may decrease lamotrigine exposure *[see Clinical Pharmacology (12.3)]*, which may reduce efficacy of lamotrigine.
Prevention or Management	Adjust lamotrigine dosage as recommended in its Prescribing Information based on NEXTSTELLIS initiation or discontinuation.
Systemic Corticosteroids	
Clinical Effect	Concomitant use of NEXTSTELLIS may increase the exposure of certain systemic corticosteroids, which may increase the risk of corticosteroid-related adverse reactions [*see Clinical Pharmacology (12.2*).
Prevention or Management	Follow the recommendation for the corticosteroid in accordance with its Prescribing Information. Consider more frequent monitoring for corticosteroid adverse reactions when used concomitantly with NEXTSTELLIS.

Thyroid Hormone Replacement Therapy	
Clinical Effect	*Concomitant use of NEXTSTELLIS may increase thyroid-binding globulin concentration [see Warnings and Precautions (5.10) and Clinical Pharmacology (12.2)].*
Prevention or Management	*Monitor thyroid-stimulating hormone (TSH) level and follow the recommendation for thyroid hormone replacement in accordance with its Prescribing Information.*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Discontinue NEXTSTELLIS if pregnancy occurs, because there is no reason to use hormonal contraceptives during pregnancy *[see Contraindications (4)]*. 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. Reproductive toxicity studies performed with E4 alone have shown expected pharmacologic effects in animals, which are considered consistent with estrogen exposure.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4 percent and 15 to 20 percent, respectively.

8.2 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 woman to use other methods of contraception until she discontinues breast-feeding *[see also Dosage and Administration (2.1)]*. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for NEXTSTELLIS and any potential adverse effects on the breast-fed child from NEXTSTELLIS or from the underlying maternal condition.

After oral administration of /DRSP 3 mg/EE 30 μg, about 0.02% of the DRSP dose was excreted into the breast milk of postpartum females within 24 hours. This results in a potential maximal daily dose of less than 1 μg DRSP in an infant.

8.4 Pediatric Use

Safety and efficacy of NEXTSTELLIS have been established in females of reproductive potential. The study population of C302 *[see Clinical Studies (14)]* was in females of reproduction age 16-50 years of age. Use of NEXTSTELLIS before menarche is not indicated.

8.5 Geriatric Use

NEXTSTELLIS has not been studied in postmenopausal females and is not indicated in this population.

8.6 Hepatic Impairment

NEXTSTELLIS is contraindicated in females with hepatic impairment *[see Contraindications (4), Warnings and Precautions (5.1, 5.3)]***.** The mean exposure to drospirenone (DRSP) in females with moderate liver impairment is approximately three times higher than the exposure in females

with normal liver function. NEXTSTELLIS has not been studied in females with severe hepatic impairment *[see Clinical Pharmacology (12.3)].*

8.7 Renal Impairment
NEXTSTELLIS is contraindicated in females with renal impairment *[see Contraindications (4), Warnings and Precautions (5.1)*].

In subjects with creatinine clearance (CLcr) of 50–79 mL/min, serum DRSP levels were comparable to those in a control group with CLcr ≥ 80 mL/min. In subjects with CLcr of 30–49 mL/min, serum DRSP concentrations were on average 37% higher than those in the control group. In addition, there is a potential to develop hyperkalemia in subjects with renal impairment whose serum potassium is in the upper reference range, and who are concomitantly using potassium sparing drugs *[see Warnings and Precautions (5.2), Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

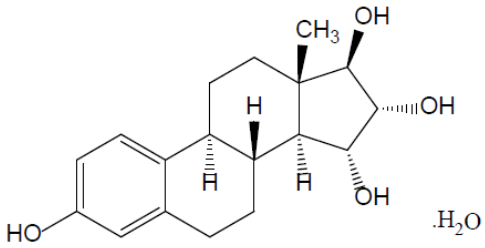
8.8 Race/Ethnicity
No clinically significant difference was observed between the pharmacokinetics of E4 or DRSP depending on race *[see Clinical Pharmacology (12.3)]*.

8.9 Body Mass Index (BMI)/Body Weight
The safety and efficacy of NEXTSTELLIS in females with a BMI ≥ 35 kg/m^2 have not been adequately evaluated.

10 OVERDOSAGE
Overdosage of CHCs may cause nausea, vomiting, and severe headaches. Individual reports of thromboembolic complications and vaginal bleeding have occurred from overdosage. Pediatric patients with unintended CHC ingestion have reported nausea and vomiting and some developed irritability and drowsiness; rare reports described vaginal bleeding.

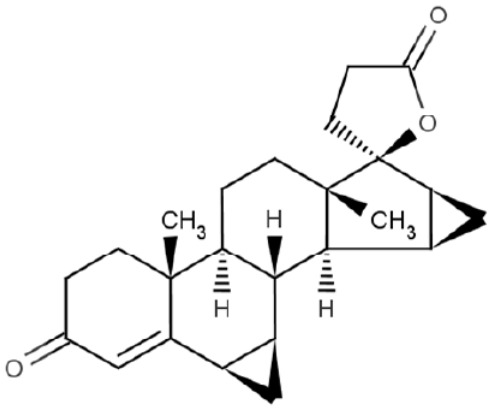
Overdosage Management Recommendations
Consider short-term prophylactic anticoagulation therapy for patients with high risk of VTE.
Monitor serum potassium and sodium levels, and for evidence of metabolic acidosis.

11 DESCRIPTION
NEXTSTELLIS™ (drospirenone and estetrol tablets) is an oral contraceptive. It is supplied in a transparent PVC/aluminum blister cards containing 28 tablets:
• 24 pink active tablets contain 3 mg drospirenone and 14.2 mg of estetrol on the anhydrous basis. Drospirenone is a synthetic progestin and estetrol is a synthetic estrogen.
• 4 white inert tablets.
The chemical name for estetrol is estra-1,3,5(10)-triene-3,15α,16α,17α-tetrol monohydrate. It has a molecular formula of $C_{18}H_{24}O_4 \cdot H_2O$ and a molecular weight of 322.4 g/mol, equivalent to 304.4 g/mol (anhydrous). Estetrol has the following chemical structure:



Estetrol (monohydrate) is a white to off-white crystalline solid that is poorly soluble in water and aqueous solutions. It is soluble in methanol, ethanol, sparingly soluble in acetone, and slightly soluble in ethyl acetate and acetonitrile.

Drospirenone is chemically described as (6R,7R,8R,9S,10R,13S,14S,15S,16S,17S)-1,3',4',6,6a,7,8,9,10,11,12,13,14,15,15a,16-hexadecahydro10,13-dimethylspiro-[17H-dicyclopropa-[6,7:15,16]cyclopenta[a]phenanthrene-17,2'(5H)-furan]-3,5'(2H)-dione). It has a molecular weight of 366.5 g/mol, a molecular formula of $C_{24}H_{30}O_3$, and the structural formula below:



Drospirenone is a white to almost white or slightly yellow crystalline powder. It is a neutral molecule with slight solubility in water.

The active tablet is a 6 mm, round pink film-coated tablet which contains 3 mg of drospirenone and 15 mg of estetrol as the monohydrate, equivalent to 14.2 mg of estetrol on the anhydrous basis, and the following inactive ingredients: corn starch, lactose monohydrate, magnesium stearate, povidone, and sodium starch glycolate, , and . Each tablet is embossed on one side with a drop-shaped logo. The pink film-coating has the following inactive ingredients: hydrogenated cottonseed oil, hydrogenated cottonseed oil, hydroxypropylcellulose, hypromellose, iron oxide red, talc, and titanium dioxide

The inert tablet is a 6 mm, round white film-coated tablet which contains the inactive ingredients corn starch, lactose monohydrate, and magnesium stearate. Each tablet is embossed on one side with a drop-shaped logo. The film-coating has the following inactive ingredients: hydrogenated cottonseed oil, hydroxypropylcellulose, hypromellose, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CHCs prevent pregnancy primarily by suppressing ovulation.

12.2 Pharmacodynamics

Drospirenone is a spironolactone analogue with anti-mineralocorticoid and antiandrogenic activity. The estrogen in NEXTSTELLIS is estetrol, a synthetic analogue of a native estrogen present during pregnancy, that is selective for nuclear estrogen receptor-α (ER-α) and ER-β.

Effect of NEXTSTELLIS on ovarian function

A clinical study evaluated the effect of NEXTSTELLIS on the suppression of ovarian activity as assessed by measurement of follicle size via transvaginal ultrasound and serum hormone (progesterone and estradiol) analyses in two of the three treatment cycles (24-day active tablet period plus 4-day pill-free period). No ovulations were observed during the study.

Cardiac Electrophysiology

At a dose 5 times the maximum recommended dose (i.e., supra-therapeutic dose of 15 mg DRSP /71 mg E4), NEXTSTELLIS does not prolong the QT interval to any clinically relevant extent.

Drugs That Have the Potential to Increase Serum Potassium Concentration

There is a potential for an increase in serum potassium concentration in females taking NEXTSTELLIS with other drugs that may increase serum potassium concentration [see Warnings and Precautions (5.2)].

A drug-drug interaction study of DRSP 3 mg /E2 1 mg versus placebo was performed in 24 mildly hypertensive postmenopausal females taking enalapril maleate 10 mg twice daily. Potassium concentrations were obtained every other day for a total of 2 weeks in all subjects. Mean serum potassium concentrations in DRSP/E2 treatment group relative to baseline were 0.22 mEq/L higher than those in the placebo group. Serum potassium concentrations also were measured at multiple time points over 24 hours at baseline and on Day 14. On Day 14, the ratios for serum potassium C_{max} and AUC in the DRSP/E2 group to those in the placebo group were 0.955 (90% CI: 0.914, 0.999) and 1.010 (90% CI: 0.944, 1.08), respectively. No patient in either treatment group developed hyperkalemia (serum potassium concentrations > 5.5 mEq/L).

Other PD effects of NEXTSTELLIS

Table 7 displays pharmacodynamic effects of CHCs on hemostatic, metabolic, and endocrine parameters.

Table 7: Pharmacodynamics Effects of CHCs on Hemostatic, Metabolic, and Endocrine Parameters

Category	Direction of Change[1]		
	Increase	Decrease	No change
Coagulation Factors	↑ Platelet count; factors II, VII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, and beta-thromboglobulin; fibrinogen and fibrinogen activity; plasminogen antigen and activity	↓(Accelerated) Prothrombin time, partial thromboplastin time, and platelet aggregation time ↓ Anti-factor Xa and antithrombin III, antithrombin III activity	

Corticosteroids	↑ Corticosteroid-binding globulin (CBG), total circulating corticosteroids	-	-
Glucose	-	↓ Glucose tolerance	-
Lipids	↑	↓ Low-density lipoprotein concentration	Plasma high-density lipoprotein (HDL) and HDL2 cholesterol subfraction concentration, triglyceride levels
Mineralocorticoids	↑ Aldosterone		
Plasma proteins	↑ Concentrations of angiotensinogen/renin substrate, alpha-1 antitrypsin, ceruloplasmin	-	-
Sex hormones	↑ Sex hormone-binding globulin (SHBG)	↓ Possible decreased free testosterone concentrations ↓ Androstenedione, progesterone, free testosterone, estradiol	DHEA-S, FSH, LH, Dihydrotestosterone
Thyroid hormones	↑ Thyroxin-binding globulin (TBG), total thyroid hormone levels, total T4 and T3 levels	↓ T3 resin uptake	↔ TSH, Free T4 and free T3 concentrations in females with normal thyroid function

12.3 Pharmacokinetics

Absorption, Distribution, Metabolism, and Excretion

The pharmacokinetic properties of E4 and DRSP following administration of NEXTSTELLIS are provided in TABLE 8.

Table 8. Pharmacokinetics of E4 and DRSP

	E4	**DRSP**
Multiple-dose pharmacokinetics parameters		
Mean (CV%) C_{max}, ng/mL	17.9 (68.1)	48.7 (24.6)
Mean (CV%) AUC_{0-24h}, ng*hr/mL	59.1 (24.3)	519.0 (27.7)
Dose Proportionality	15 mg to 75 mg	1-10 mg
Time to Steady State, days	4	10
Accumulation Ratio	1.6	2.3
Absorption		

Median (range) T_{max}, hours	0.5 (0.5 to 2)	1.0 (1.0 to 3.0)
Effect of high-fat meal (relative to fasting)		
Geometric Mean (90% CI) $C_{max,}$ Ratio	0.51 (0.37, 0.70)	0.75 (0.66, 0.84)
Geometric Mean (90% CI) $AUC_{0\text{-}INF,}$ Ratio	1.01 (0.86, 1.19)	1.08 (1.02, 1.14)
Distribution		
Plasma Protein Binding	46% to 50%	95% to 97%[a]
Elimination		
Elimination Half-life, hours	27[b]	34
Metabolism		
Primary Pathways	Phase 2 metabolism to form glucuronide and sulphate conjugates which have negligible in-vitro estrogenic activity. In vitro studies show that UGT2B7 is the dominant UGT isoform that catalyzes the formation of E4-16-glucuronide	CYP3A4; two main metabolites: acid form of DRSP generated by opening of lactone ring and the 4,5-dihydrodrospirenone formed by reduction followed by sulfation. Both metabolites are not pharmacologically active.
Excretion		
Primary Pathways		
% Dose in Urine	69% (0% unchanged)	38%
% Dose in Feces	22% (100% unchanged)	44%

[a] Bound primarily to albumin
[b] Undergoes enterohepatic recycling

C_{max}= Maximum plasma concentration; $AUC_{0\text{-}t}$= Area under the plasma concentration-time curve integrated from time of administration (0) to time of last quantifiable observation (t); $AUC_{0\text{-}INF}$= Area under the plasma concentration-time curve from time of administration extrapolated to infinity from $AUC_{0\text{-}t}$; CI= Confidence interval; T_{max}= Time to maximum concentration

Specific Populations

No clinically significant differences in the pharmacokinetics of E4 or DRSP in females were observed based on race/ethnicity (Japanese and Caucasian).

Patients with Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of E4 is unknown.

The mean exposure to DRSP is approximately three times higher in females with moderate liver impairment than the exposure in females with normal liver function. The effect of severe hepatic impairment on the pharmacokinetics of DRSP is unknown.

Patients with Renal Impairment
The effect of renal impairment on the pharmacokinetics of E4 is unknown. The mean serum DRSP concentrations increased by 37% in subjects with CLcr of 30 to 49 mL/min on a low potassium diet using potassium-sparing drugs. No clinically significant differences in the pharmacokinetics of DRSP were observed based on CLcr of 50 to 79 mL/min. DRSP treatment did not show any clinically significant effect on serum potassium concentration. Although hyperkalemia was not observed in the study, in five of the seven subjects who continued use of potassium-sparing drugs during the study, mean serum potassium concentrations increased by up to 0.33 mEq/L.

Drug Interaction Studies
Clinical Studies

Strong CYP3A4 Inhibitor: Concomitant use of a COC containing DRSP 3 mg/EE 20 μg with ketoconazole (strong CYP3A4 inhibitor) increased the AUC_{0-24h} and C_{max} of DRSP by 2.68-fold (90% CI: 2.44, 2.95) and 1.97-fold (90% CI: 1.79, 2.17), respectively.

CYP3A4 Inducer: Concomitant use of a COC containing DRSP 3 mg/EE 20 μg with high dose (strong CYP3A induction) and low dose of rifampin (weak CYP3A4 induction) decreased the AUC_{0-24h} of DRSP by 86% (90% CI: 85%, 87%) and 30% (90% CI: 25%, 34%), respectively.

UGT2B7 Inhibitor: No clinically significant differences in the pharmacokinetics of NEXTSTELLIS were observed when used concomitantly with valproic acid (UGT2B7 inhibitor).

CYP3A Substrate: Pharmacokinetics of CYP3A substrates midazolam and simvastatin were not influenced by steady state DRSP concentrations achieved after administration of 3 mg DRSP/day.

CYP2C19 Substrate: Daily oral administration of 3 mg DRSP for 14 days did not affect the oral clearance of the CYP2C19 substrate omeprazole (40 mg, single oral dose) and the CYP2C19 product 5-hydroxy omeprazole.

In Vitro Studies
E4 is not a substrate of CYP1A1, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP3A4, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2-K. E4 is unlikely to induce CYP1A2, CYP2B6, CYP3A4 or inhibit CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, UGT1A9, UGT2B7, drug transporters P-pg, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K or at clinically relevant dose.

Effects of NEXTSTELLIS on Lamotrigine
Estrogens are known to decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. No in vitro or in vivo data are available to determine the impact of E4 on lamotrigine exposure.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month oral carcinogenicity study in mice with doses up to 10 mg/kg/day DRSP, equating to 2 times the maximum clinical exposure (based on AUC), there was an increase in carcinomas of the harderian gland in the high dose DRSP group. In a similar study in rats given doses up to 10 mg/kg/day DRSP, 10 times the maximum clinical exposure (based on AUC), there was an increased incidence of benign and total (benign and malignant) adrenal gland pheochromocytomas in the high dose DRSP group.

Mutagenesis studies for DRSP were conducted *in vivo* and *in vitro* and no evidence of mutagenic activity was observed. E4 is not considered to be genotoxic based on weight of evidence from *in vivo* and *in vitro* mutagenesis studies.

14 CLINICAL STUDIES

Pregnancy Prevention

The efficacy of NEXTSTELLIS was evaluated in a prospective, multicenter, open-label, single-arm study in North America (NCT02817841; C302) of one-year duration that enrolled 1,674 females 16 to 35 years of age. The mean age was 25.8 years and mean BMI was 25.8 kg/m^2. Females with a BMI between 30 and 35 kg/m^2 accounted for 22.3% of the study population. Females with a BMI greater than 35 kg/m^2 were not enrolled in the study. The racial distribution was 70.1% Caucasian, 19.5% Black or African American, 4.8% Asian, 0.9% American Indian or Alaska native, 0.4% Native Hawaiian or other Pacific Islander and 4.2% other.

A total of 26 on-treatment pregnancies occurred in 1,524 females contributing 12,763 at-risk cycles. The overall Pearl Index was 2.65 (95% CI: 1.73-3.88) per 100 woman-years of use. Table 9 lists the Pearl Index by BMI subgroup. A trend of decreasing effectiveness with increasing BMI was observed in the study.

Table 9 Pearl Index Based on At-Risk Cycles and Reported Pregnancies in Females ≤ 35 Years of Age in Study C302

Subgroup	N*	On-treatment pregnancies	At-risk cycles	Pearl Index (95% CI)
Study C302	1524	26	12,763	2.65 (1.73, 3.88)
BMI (kg/m^2)				
< 30	1,187	20	10,113	2.57 (1.57, 3.97)
≥ 30 to < 35**	337	6	2,650	2.94 (1.08, 6.41)

* N = all females aged 16-35 with at least 1 at-risk cycle.
**One female with a BMI of 48 kg/m^2 was enrolled and included in the efficacy analysis.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

NEXTSTELLIS (drospirenone and estetrol tablets) is available in a blister card, with 28 6-mm round, bi-convex film-coated tablets in the following order:

- 24 pink active film-coated tablets containing 3 mg drospirenone and 14.2 mg estetrol embossed with a drop-shaped logo on one side.
- 4 white inert film-coated tablets embossed with a drop-shaped logo on one side.

NEXTSTELLIS is supplied in cardboard cartons containing 1 blister card of 28 tablets: NDC **51862-258-01.**

16.2 Storage

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

16.3 Disposal

Dispose unused medication via a take-back option if available. Otherwise, follow FDA instructions for disposing medication in the household trash, www.fda.gov/drugdisposal. Do NOT flush down the toilet.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-Approved patient labeling (Patient Information and Instructions of Use).

Sexually Transmitted Infections

Advise females that NEXTSTELLIS does not protect against HIV infection or other sexually transmitted infections.

Important Administration Instructions and Instructions for Missed Doses

Instruct females to take one tablet daily by mouth at the same time every day. Advise patients about what to do in the event that pills are missed *[see Dosage and Administration (2.3)]*.

- Advise females starting NEXTSTELLIS to use additional nonhormonal contraception for 7 days after the first dose unless NEXTSTELLIS is started on the first day (Day 1) of menses *[see Dosage and Administration (2.1)]*
- Advise females who miss more than two consecutive days of NEXTSTELLIS or experience vomiting or diarrhea for > 48 hours consecutively to use additional nonhormonal contraception for 7 days *[see Dosage and Administration (2.3, 2.4)]*

Thromboembolic Disorders and Other Vascular Problems *[see Warnings and Precautions (5.1)]*.

- Advise females that there is an increased risk of arterial and/or venous thrombotic/thromboembolic events with NEXTSTELLIS and the risk of arterial and/or venous thrombotic/thromboembolism is greater in smokers and females with preexisting medical conditions including hypertension, dyslipidemia, diabetes, and obesity.
- Advise patients of the pertinent factors that further increase their risk and ways to diminish the risk, e.g., to stop smoking (if applicable).
- Advise patients to contact their healthcare professional for any signs or symptoms of arterial and/or VTE
- Advise patients to contact their healthcare professional if they will be immobilized for a prolonged period of time.

Hyperkalemia

Advise females to contact their healthcare professional if signs or symptoms of hyperkalemia develop *[see Warnings and Precautions (5.2)]*.

Hypertension

Advise females that NEXTSTELLIS can cause an increase in blood pressure over time. Instruct patients to contact their healthcare professional if blood pressure increases *[see Warnings and Precautions (5.3)]*.

Liver Disease

Advise females that use of NEXTSTELLIS can cause elevated liver enzymes and can increase the risk of liver tumors. Instruct females to contact their healthcare professional for any signs or symptoms of liver disease *[see Warnings and Precautions (5.5)]*.

Glucose Tolerance

Advise females that NEXTSTELLIS may decrease glucose tolerance. Instruct females with diabetes and prediabetes to contact their healthcare professional for any signs or symptoms of hyperglycemia *[see Warnings and Precautions (5.7) and Clinical Pharmacology (12.2)]*.

Gallbladder Disease and Cholestasis

Advise females that use of NEXTSTELLIS is associated with an increased risk of developing and/or worsening gallbladder disease. Instruct patients to contact their healthcare professional for any signs or symptoms of gallbladder disease *[see Warnings and Precautions (5.8)].*

Bleeding Irregularities, Amenorrhea, and Pregnancy

Advise females that NEXTSTELLIS can cause unscheduled bleeding and spotting, as well as amenorrhea and oligomenorrhea. Advise females to contact their health care professional if amenorrhea occurs in two or more consecutive cycles or symptoms of pregnancy occur, e.g., morning sickness or unusual breast tenderness. Instruct females to stop NEXTSTELLIS if pregnancy is confirmed during use *[see Warnings and Precautions (5.11) and Use in Specific Populations (8.1)]*.

Chloasma

Advise females that NEXTSTELLIS can cause chloasma and the risk is highest in females with a history of chloasma, especially chloasma gravidarum. Instruct females to take precautions to limit UVA and UVB exposure while using NEXTSTELLIS *[see Warnings and Precautions (5.14)]*.

Lactation

Advise postpartum females that NEXTSTELLIS may reduce breast milk production. Advise females that this reduction is less likely to occur if breast-feeding is well established *[see Use in Specific Populations (8.2)].*

Drug Interactions

NEXTSTELLIS may interact with many drugs, foods, and dietary supplements. Therefore, advise females to report to their healthcare professional the use of any other prescription or nonprescription drugs or dietary supplements *[see Drug Interactions (7.1, 7.2)]*.

Manufactured for:
Mayne Pharma LLC
1240 Sugg Parkway
Greenville, NC 27834

Manufactured in Germany

Date: 04/2022

PATIENT INFORMATION
NEXTSTELLIS (NEXT ste LIS)
(drospirenone and estetrol tablets)
for oral use

What is the most important information I should know about NEXTSTELLIS?

Do not use NEXTSTELLIS if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects (heart and blood vessel problems) from birth control pills, including death from heart attack, blood clots or stroke. The risk increases with age and the number of cigarettes you smoke.

What is NEXTSTELLIS?

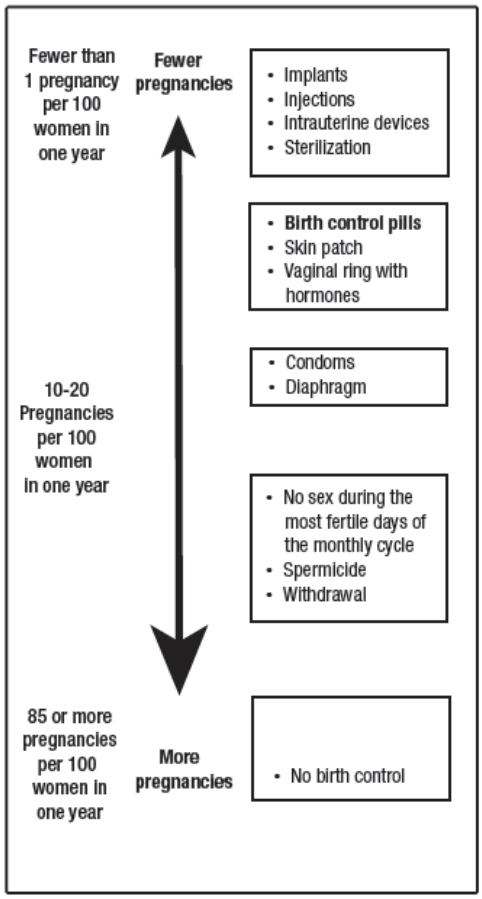
- NEXTSTELLIS is a birth control pill (oral contraceptive) used by females to prevent pregnancy.
- NEXTSTELLIS does not protect against HIV infections (AIDS) and other sexually transmitted infections.
- NEXTSTELLIS may be less effective if you have a body mass index (BMI) of 30 or higher. In females with a BMI of 30 or higher, NEXTSTELLIS may become less effective as your BMI increases.
- It is not known if NEXTSTELLIS is safe and effective in females with a BMI of 35 or higher.

How does NEXTSTELLIS work for contraception?

Your chance of getting pregnant depends on how well you follow the directions for taking your birth control pills. The better you follow the directions, the less chance you have of getting pregnant.

Based on the results of one clinical study of a 2 regimen of drospirenone 3 mg and estetrol 14.2 mg tablets, about 2 out of 100 females may get pregnant within the first year they use NEXTSTELLIS.

The following chart shows the chance of getting pregnant for females who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for females who do not use birth control and are trying to get pregnant.



Do not take NEXTSTELLIS if you:

- smoke and are 35 years of age and older.
- have or have had blood clots in your arms, legs, lungs, or eyes.
- have a problem with your blood that makes it clot more than normal.
- have certain heart valve problems or an irregular heart beat that increases your risk of having blood clots.
- had a stroke.

- had a heart attack.
- have high blood pressure that cannot be controlled by medicine or have high blood pressure with blood vessel problems.
- have diabetes:
  - with high blood pressure or kidney, eye, nerve, or blood vessel damage, **or**
  - for more than 20 years.
- have certain kinds of severe migraine headaches with aura.
- have liver problems, including liver tumors.
- have any unexplained vaginal bleeding.
- have or have had breast cancer or any cancer that is sensitive to female hormones.
- have kidney disease or kidney failure.
- have reduced adrenal gland function (adrenal insufficiency).
- 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.

If any of these conditions happen while you are taking NEXTSTELLIS, stop taking NEXTSTELLIS right away and talk to your healthcare provider. Use non-hormonal contraception when you stop taking NEXTSTELLIS.

Before taking NEXTSTELLIS, tell your healthcare provider about all of your medical conditions, including if you:

- are scheduled for surgery. NEXTSTELLIS may increase your risk of blood clots after surgery. Talk to your healthcare provider about taking NEXTSTELLIS before and after your surgery or if you are going to be unable to walk for an extended period of time (immobilized).
- are depressed now or have been depressed in the past.
- had yellowing of your skin or eyes (jaundice) caused by pregnancy (cholestasis of pregnancy).
- are pregnant or think you may be pregnant.
- are breastfeeding or plan to breastfeed. NEXTSTELLIS may decrease the amount of breast milk you make. NEXTSTELLIS may pass into your breast milk. Talk to your healthcare provider about the best birth control method for you while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. If you are currently on daily, long-term treatment for a chronic condition with any of the following medicines, you should talk to your healthcare provider before taking NEXTSTELLIS:

- CYP inducers (aprepitant, barbituates, bosentan, carbamazepine, efavirenz, felbamate, griseofluvin, oxycarbazepine, phenytoin, rifamptin, ribatin, topiramate, products containing St. John's wort, and others)
- CYP inhibitors (itraconazole, voriconazole, fluconazole, ketoconazole and others)
- HIV/hepatitis C virus protease inhibitors and non-nucleoside reverse transcriptase inhibitors (nelfinavir, ritonavir, boceprevir, telaprevir, indinavir, nevirapine, etravirine and others)
- Lamotrigine
- Potassium-sparing diuretics (spironolactone and others)
- Potassium supplementation
- Corticosteroids

NEXTSTELLIS may affect the way other medicines work, and other medicines may affect how well NEXTSTELLIS works.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take NEXTSTELLIS?

- **Read the detailed Instructions for Use at the end of this Patient Information leaflet about the right way to take your NEXTSTELLIS.**

What are the possible side effects of NEXTSTELLIS?

- **, NEXTSTELLIS may cause serious side effects including blood clots in your lungs, heart attack, or a stroke that may lead to death. Some other examples of serious blood clots include blood clots in the legs or eyes.** Serious blood clots can happen especially if you smoke, are obese, have high blood pressure, have diabetes, have high cholesterol, or are older than 35 years of age. Serious blood clots are more likely to happen when you:
  - first start taking birth control pills
  - restart the same or different birth control pills after not using them for a month or more

Call your healthcare provider or go to a hospital emergency room right away if you have:

- leg pain that will not go away
- sudden severe shortness of breath
- sudden change in vision or blindness
- chest pain
- a sudden, severe headache unlike your usual headaches
- weakness or numbness in your arm or leg

- trouble speaking

Other serious side effects include:

- **high potassium levels in your blood (hyperkalemia).** Certain medicines and conditions can also increase the potassium levels in your blood. Your healthcare provider may check the potassium levels in your blood during treatment with NEXTSTELLIS. Call your healthcare provider or go to a hospital emergency room right away if you have signs or symptoms of high potassium levels in your blood including:
  - weakness or numbness in an arm or leg
  - palpitations (feel like your heart is racing or fluttering) or irregular heartbeat
  - nausea
  - vomiting
  - severe pain in your chest
  - shortness of breath
- **high blood pressure.** You should see your healthcare provider to check your blood pressure regularly.
- **new or worsening headaches including migraine headaches.**
- **possible cancer that is sensitive to female hormones, such as breast cancer, skin cancer (melanoma), lung cancer, and brain cancer.**
- **liver problems, including:**
  - an increase in liver enzymes in the blood
  - rare liver tumors
  - jaundice. Call your healthcare provider if you have yellowing of your skin or eyes.
- **changes in the sugar and fat (cholesterol and triglycerides) levels in your blood.**
- **gallbladder problems (cholestasis),** especially if you previously had cholestasis of pregnancy.
- **irregular or unusual vaginal bleeding or spotting between your menstrual periods, especially during the first 4 months of taking NEXTSTELLIS, or the absence of menstrual periods.**
- **Depression.**
- **possible cancer in your cervix.**
- **swelling of your skin especially around your mouth, eyes, and in your throat (angioedema).** Call your healthcare provider right away if you have a swollen face, lips, mouth tongue or throat, which may lead to difficulty swallowing or breathing. Your chance of having angioedema is higher if you have a history of angioedema.
- **dark patches of skin around your forehead, nose, cheeks and around your mouth, especially during pregnancy (chloasma).** Females who tend to get chloasma should avoid spending a long time in sunlight, tanning booths, and under sun lamps while taking NEXTSTELLIS. Use sunscreen if you have to be in the sunlight.

What are the most common side effects of NEXTSTELLIS?

The most common side effects of NEXTSTELLIS include:

- irregular vaginal bleeding (including absence of period)
- headache
- acne
- pain with your periods
- breast tenderness, pain and discomfort
- weight gain
- mood changes
- decreased sex drive

These are not all of the possible side effects of NEXTSTELLIS.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Do birth control pills cause cancer?

It is not known if hormonal birth control pills causes breast cancer. Some studies, but not all, suggest that there could be a slight increase in the risk of breast cancer among current users with longer duration of use.
If you have breast cancer now, or have had it in the past, do not use hormonal birth control because some breast cancers are sensitive to hormones.
Females who use birth control pills may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

What if I want to become pregnant?

You may stop taking the pill whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop taking the pill.

What should I know about my period when taking NEXTSTELLIS?

Irregular vaginal bleeding or spotting may happen while you are taking NEXTSTELLIS, especially during the first 4 months of use. If the irregular vaginal bleeding or spotting continues or happens again after you have had regular menstrual cycles, call your healthcare provider. It is important to continue taking your pills on a regular schedule to prevent a pregnancy.

What if I miss my scheduled period when taking NEXTSTELLIS?

Some females miss periods on hormonal birth control, even when they are not pregnant. However, if you go 2 or more months in a row without a period, or you miss your period after a month where you did not take all of your NEXTSTELLIS correctly, call you healthcare provider because you may be pregnant. Also call your healthcare provider if you have symptoms of pregnancy such as morning sickness or unusual breast tenderness. Stop taking NEXTSTELLIS if you are pregnant.

What else should I know about taking NEXTSTELLIS?

- If you are scheduled for any lab tests, tell your healthcare provider you are taking NEXTSTELLIS. Certain blood tests may be affected by NEXTSTELLIS.

How should I store NEXTSTELLIS?

- Store NEXTSTELLIS at room temperature between 68°F to 77°F (20°C to 25°C).
- Throw away unused NEXTSTELLIS through a take-back option, if available. You may also visit www.fda.gov/drugdisposal for FDA instructions for throwing away medicine in your household trash. Do not flush NEXTSTELLIS down the toilet.
- Keep NEXTSTELLIS and all medicines out of the reach of children.

General information about the safe and effective use of NEXTSTELLIS.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use NEXTSTELLIS for a condition for which it was not prescribed. Do not give NEXTSTELLIS to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about NEXTSTELLIS that is written for health professionals.

What are the ingredients in NEXTSTELLIS?

Active ingredient: Pink tablets: **drospirenone and estetrol**

Inactive ingredients:

- Pink tablets: lactose monohydrate, sodium starch glycolate, corn starch, povidone and magnesium stearate.
- White tablets: lactose monohydrate, corn starch and magnesium stearate.
- Film coating: hydroxypropylmethylcellulose, hydroxypropylcellulose, talc, hydrogenated cottonseed oil, and titanium dioxide.

For more information, go to www.maynepharma.com or call 1-844-825-8500