

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

**NEXTSTELLIS**

Estetrol monohydrate and Drospirenone Tablets

15 mg estetrol monohydrate and 3 mg drospirenone tablets.

Oral Contraceptive

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## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATION

NEXTSTELLIS (estetrol monohydrate and drospirenone) is indicated for:

- Prevention of pregnancy

#### 1.1 Pediatrics

**Pediatrics (< 16 years of age):** Safety and efficacy have been studied in women between 16 and 50 years old. No data in women under 16 are available to Health Canada. Therefore, Health Canada has not authorized an indication for pediatric use. Use of this product before menarche is not indicated.

#### 1.2 Geriatrics

**Geriatrics:** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for women over 50 years of age. NEXTSTELLIS is not indicated for use in postmenopausal women.

### 2 CONTRAINDICATIONS

NEXTSTELLIS is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

NEXTSTELLIS should not be used in women with the following conditions:

- a history of or actual thrombophlebitis or thromboembolic disorders (such as deep vein thrombosis or pulmonary embolism);
- presence of severe or multiple risk factor(s) for arterial or venous thrombosis (see **WARNINGS AND PRECAUTIONS - Risk factors for VTE** and **Risk factors for ATE**), such as:
  - hypertension
  - hereditary or acquired predisposition for venous or arterial thrombosis, such as Factor V Leiden mutation and activated protein C (APC-) resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia and antiphospholipid-antibodies (anticardiolipin antibodies, lupus anticoagulant) and prothrombin mutation G20210A
  - severe dyslipoproteinemia
  - diabetes mellitus with vascular involvement
  - increasing age, particularly above 50 years
  - obesity
  - other medical conditions associated with venous thromboembolism or other adverse vascular events
  - positive family history (arterial thromboembolism in a sibling or parent especially at relatively early age, e.g., below 50)
  - prolonged immobilization, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma

- smoking, particularly in women who are over 35 years of age
- a history of or actual cerebrovascular disorders;
- a history of or actual myocardial infarction or coronary artery disease;
- valvular heart disease with complications;
- history of or actual prodromi of a thrombosis (e.g., transient ischaemic attack, angina pectoris);
- active liver disease, or history of or actual benign or malignant liver tumours;
- known or suspected carcinoma of the breast;
- carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia;
- undiagnosed abnormal vaginal bleeding;
- steroid-dependent jaundice, cholestatic jaundice, history of jaundice of pregnancy;
- any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields;
- known or suspected pregnancy;
- current or history of migraine with focal aura;
- history of or actual pancreatitis if associated with severe hypertriglyceridaemia;
- renal insufficiency;
- hepatic dysfunction;
- adrenal insufficiency.

### 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

#### Serious Warnings and Precautions

Cigarette smoking increases the risk of serious cardiovascular events associated with the use of hormonal contraceptives. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, NEXTSTELLIS should not be used by women who are over 35 years of age and smoke (see **WARNINGS AND PRECAUTIONS, Cardiovascular**).

Patients should be counselled that birth control pills **DO NOT PROTECT** against sexually transmitted infections (STIs) including HIV/AIDS. For protection against STIs, it is advisable to use latex or polyurethane condoms **IN COMBINATION WITH** birth control pills.

### 4 DOSAGE AND ADMINISTRATION

#### 4.1 Dosing Considerations

Pregnant women: NEXTSTELLIS should not be used in women who are pregnant.

Hepatic impairment: No clinical studies have been performed with NEXTSTELLIS in patients with hepatic insufficiency. NEXTSTELLIS is contraindicated in women with moderate to severe hepatic diseases.

Renal impairment: NEXTSTELLIS has not been specifically studied in patients with renal impairment. As drospirenone has anti-mineralocorticoid activity there is a potential for

hyperkalemia in high-risk patients, NEXTSTELLIS is contraindicated in women with moderate to severe renal insufficiency.

Concomitant medications: Please see **DRUG-DRUG INTERACTION** section.

## **4.2 Recommended Dose and Dosage Adjustment**

Take one tablet by mouth at the same time every day. The failure rate may increase when pills are missed or taken incorrectly.

It is recommended that NEXTSTELLIS tablets should be taken every day at about the same time regardless of mealtimes and as directed on the package. Stickers marked with the 7 days of the week are provided, and the relevant weekday sticker should be stuck on the tablet blister as an indicator of when the first tablet has been taken.

## **4.3 Administration**

Each pack starts with 24 pink active tablets, followed by 4 white inert tablets. One hormone-containing pink tablet is taken each day for 24 consecutive days, followed by one hormone-free white tablet for 4 days. Tablets should be taken at about the same time every day. The next pack is started immediately after finishing the previous one on the same day of the week that the first course was started, without a break and irrespective of the presence or absence of withdrawal bleeding. Withdrawal bleeding usually starts 2 to 4 days after the last pink tablet, i.e., when taking the second, third or fourth white tablet, and may not have finished before the next pack is started.

### **How to Start NEXTSTELLIS (No preceding hormonal contraceptive use in the past month)**

The patient may begin using NEXTSTELLIS on day 1 of her menstrual cycle (i.e., the first day of menstrual flow) or on the first Sunday after her period begins. NEXTSTELLIS is effective from the first day of therapy if the tablets are begun on the first day of the menstrual cycle. If the first NEXTSTELLIS tablet is taken later than Day 1 of the menstrual cycle, an additional barrier method of birth control, such as a condom, is recommended for the first 7 days of use.

### **Changing from another Combined Oral contraceptives (COCs)**

NEXTSTELLIS should be started on the day when the new pack of the previous COC would have started.

### **Changing from a progestogen-only-method (minipill, implant, injectable) or from a hormonal intrauterine system (IUS)**

Changing to NEXTSTELLIS can be done at any time by stopping the minipill and starting NEXTSTELLIS the next day. An implant or IUS can be removed on any day, and NEXTSTELLIS should be started that same day. When changing from an injectable contraceptive, NEXTSTELLIS should be started on the day the next injection would have been due. In all of these cases, it is advisable to additionally use a reliable barrier method such as a condom until 7 consecutive days of pink active tablet-taking are completed.

### **Following first-trimester abortion**

NEXTSTELLIS can be started immediately and no additional contraceptive measures are necessary.

### **Following delivery or second-trimester abortion**

It is advisable to start NEXTSTELLIS between Days 21 and 28 after delivery or second-trimester abortion. If starting later, it is advisable to additionally use a reliable barrier method such as a condom until 7 consecutive days of pink active tablet-taking are completed. However, if intercourse has already occurred without contraception, a further pregnancy should be excluded or the next menstrual period should begin before NEXTSTELLIS is started. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered.

For breastfeeding women see **WARNINGS AND PRECAUTIONS** section.

### **If spotting or breakthrough bleeding occurs**

Breakthrough bleeding or spotting may occur in women taking COCs, especially during the first 3 months of use. The patient is instructed to continue on the same regimen. This type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient is advised to consult her healthcare provider.

### **If withdrawal bleeding does not occur**

Although pregnancy is unlikely if NEXTSTELLIS is taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed schedule (missed one or more tablets or started taking them on a day later than she should have), the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out. Hormonal contraceptives should be discontinued if pregnancy is confirmed.

### **Advice in case of gastro-intestinal disturbances**

In case of severe gastro-intestinal disturbance (e.g. vomiting or diarrhoea), absorption of the active substances may not be complete and additional contraceptive measures should be taken.

If vomiting occurs within 4 hours after pink tablet-taking, the tablet should be considered as missed and a new tablet should be taken as soon as possible. The new tablet should be taken within 24 hours of the usual time of tablet-taking if possible. The next tablets should then be taken daily at the usual time.

If more than 24 hours elapsed since the last tablet taken, the advice concerning missed tablets is applicable (see **MISSED DOSE**). If a change to the normal tablet-taking schedule is undesirable, extra pink tablet(s) can be taken from another blister pack.

#### 4.4 Missed Dose

If you are not sure about the number or the colour of tablets missed, additionally use a reliable barrier method, such as a condom, as back-up if you have sex until you have taken active pink tablets for 7 consecutive days in a row (see What to do if you miss pills of PATIENT MEDICATION INFORMATION section).

The patient should be instructed to use the following chart if she misses 1 or more of her birth control pills. She should be told to match the number of tablets missed (one tablet, or two or more tablets) with the appropriate starting time for her dosing regimen (Sunday start or other day than Sunday) as shown below. The risk of pregnancy increases with each hormone-containing pink tablet missed.

Sunday start	Other day than Sunday start
<b><u>If one pink active tablet is missed</u></b>	
<ul style="list-style-type: none"> <li>• Take the missed tablet as soon as possible and take the next tablet at the usual time. This means that you might take two tablets on the same day.</li> <li>• Continue taking one tablet a day until the pack is finished.</li> </ul>	<ul style="list-style-type: none"> <li>• Take the missed tablet as soon as possible and take the next tablet at the usual time. This means that you might take two tablets on the same day.</li> <li>• Continue taking one tablet a day until the pack is finished.</li> </ul>
<b><u>If two or more pink active tablets are missed in a row</u></b>	
<u>From Day 1 to Day 17:</u>	<u>From Day 1 to Day 17:</u>
<ul style="list-style-type: none"> <li>• Take the last missed tablet as soon as possible and take the next tablet at the usual time. This means that you might take two tablets on the same day.</li> <li>• Continue taking one tablet a day until the pack is finished (one or more missed tablet(s) will remain in the blister pack).</li> <li>• <b>Use a back-up barrier contraception method (such as condom) if you have sex within 7 days after missing tablets.</b></li> <li>• If you missed tablets during Day 1 to Day 7 and you had unprotected sex during the 7 days preceding the first missed tablet the possibility of a pregnancy should be considered.</li> </ul>	<ul style="list-style-type: none"> <li>• Take the last missed tablet as soon as possible and take the next tablet at the usual time. This means that you might take two tablets on the same day.</li> <li>• Continue taking one tablet a day until the pack is finished (one or more missed tablet(s) will remain in the blister pack).</li> <li>• <b>Use a back-up barrier contraception method (such as condom) if you have sex within 7 days after missing tablets.</b></li> <li>• If you missed tablets during Day 1 to Day 7 and you had unprotected sex during the 7 days preceding the first missed tablet the possibility of a pregnancy should be considered.</li> </ul>
<u>From Day 18 to Day 24:</u>	<u>From Day 18 to Day 24:</u>
<ul style="list-style-type: none"> <li>• Take the last missed tablet as soon as possible and take the next tablet at the usual time. This means that you might take two tablets on the same day.</li> <li>• Continue taking one tablet per day until the next Sunday.</li> </ul>	<ul style="list-style-type: none"> <li>• Take the last missed tablet as soon as possible and take the next tablet at the usual time. This means that you might take two tablets on the same day.</li> <li>• Continue taking one tablet a day until the active pink tablets are used up.</li> <li>• Discard the four white inert tablets and start a new pack immediately.</li> </ul>

<ul style="list-style-type: none"> <li>• On Sunday, discard the pack that contains the missed tablets and start a new pack immediately.</li> <li>• <b>Use a back-up barrier contraception method (such as condom) until you have taken seven pink tablets in a row.</b></li> </ul> <p>You may not have your period this month.</p> <p><b><i>If you miss two periods in a row, the possibility of pregnancy should be considered. Contact your doctor or a clinic.</i></b></p>	<ul style="list-style-type: none"> <li>• <b>Use a back-up barrier contraception method (such as condom) if you have sex within 7 days after missing tablets.</b></li> </ul> <p>You may not have your period this month.</p> <p><b><i>If you miss two periods in a row, the possibility of pregnancy should be considered. Contact your doctor or a clinic.</i></b></p>
<b>If one or more white inert tablets are missed</b>	
<p>Skip the missed pill days and continue taking one tablet a day until the pack is finished. No additional contraception method is required.</p>	

## 5 OVERDOSAGE

On the basis of general experience with combined oral contraceptives, symptoms that may occur in association with overdose are: nausea, vomiting and vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

In a clinical pharmacology study, 1 of 32 healthy subjects receiving a suprathereapeutic dose of 75 mg E4/15 mg DRSP for 10 days experienced a deep vein thrombosis in the right lower leg. DRSP is a spironolactone analogue which has anti-mineralocorticoid properties. Serum concentration of potassium and sodium, and evidence of metabolic acidosis, should be monitored in cases of overdose.

For management of a suspected drug overdose, contact your regional poison control centre.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

NEXTSTELLIS 15 mg estetrol monohydrate / 3 mg drospirenone tablets are pink, round, biconvex film-coated tablets, with a drop-shaped logo embossed on one side.

Inert tablets are white to off-white, round, biconvex film-coated tablets, with a drop-shaped logo embossed on one side. The 4 white inert tablets do not contain active substances.

NEXTSTELLIS is available in blister strips containing 28 tablets (24 pink active estetrol monohydrate 15 mg/drospirenone 3 mg and 4 white tablets) in a carton with a storage sleeve, package insert and self-adhesive weekday stickers. The tablets are packed in thermoformed PVC-aluminum blister strips.



**Table 1: Dosage Forms, Strengths, Composition and Packaging**

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	<b>Pink active tablets</b>	
	15 mg estetrol monohydrate 3 mg drospirenone	Cottonseed oil, hydrogenated Hydroxypropylcellulose Hydroxypropylmethylcellulose Iron oxide red (E172) Lactose monohydrate Magnesium stearate (E572) Maize starch Povidone Sodium starch glycolate (Type A) Talc (E553b) Titanium dioxide (E171)
	<b>White inert tablets</b>	
	No active ingredients	Cottonseed oil, hydrogenated Hydroxypropylcellulose Hydroxypropylmethylcellulose Lactose monohydrate Magnesium stearate (E572) Maize starch Talc (E553b) Titanium dioxide (E171)

## 7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

### General

The information contained in this section is, in principle, from studies carried out in women who used combination oral contraceptives with higher strengths of estrogens and progestins than those in common use today. The effect of long-term use of combination oral contraceptives (COCs) with lower doses of both estrogen and progestin administered orally remains to be determined.

The use of COCs has been associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity and mortality is small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly if associated with the presence of other risk factors such as hypertension, hyperlipidemias, obesity, and diabetes. Other medical conditions which have been associated with adverse circulatory events include systemic lupus erythematosus, hemolytic uremic syndrome, chronic inflammatory bowel disease, (Crohn's disease or ulcerative colitis), sickle cell disease, valvular heart disease, and atrial fibrillation.

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, although a direct association with COCs has not been firmly established: porphyria,

systemic lupus erythematosus, hemolytic uremic syndrome, Sydenham's chorea, herpes gestationis, and otosclerosis-related hearing loss.

**Patients should discontinue the medication at the earliest manifestation of:**

- A. Thromboembolic and cardiovascular disorders**, such as thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, proptosis and retinal thrombosis.
- B. Conditions which predispose to venous stasis and to vascular thrombosis** (e.g., immobilization after accidents or confinement to bed during long-term illness). Other non-hormonal methods of contraception should be used until regular activities are resumed. For use of oral contraceptives when surgery is contemplated, see Perioperative Considerations, below.
- C. Visual defects- partial or complete**
- D. Papilledema or ophthalmic vascular lesions**
- E. Severe headache of unknown etiology or worsening of pre-existing migraine headache**
- F. Increase in epileptic seizures**

NEXTSTELLIS contains 3 mg of the progestin drospirenone (DRSP) that has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone. NEXTSTELLIS should not be used in patients with conditions that predispose to hyperkalemia (e.g., renal insufficiency, hepatic dysfunction, and adrenal insufficiency). Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium should have their serum potassium level checked during the first treatment cycle. Drugs that may increase serum potassium include ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, heparin, aldosterone antagonists, and NSAIDs. Consider monitoring serum potassium concentration in high-risk patients who take a strong CYP3A4 inhibitor long-term and concomitantly. Strong CYP3A4 inhibitors include azole antifungals (e.g., ketoconazole, itraconazole, voriconazole), HIV/HCV protease inhibitors (e.g., indinavir, boceprevir), and clarithromycin (see drug-drug interaction).

## **Carcinogenesis and Mutagenesis**

### **Breast Cancer**

Women who currently have or have had breast cancer should not use NEXTSTELLIS because breast cancer is a hormonally-sensitive tumour (see **CONTRAINDICATIONS**).

Increasing age and a strong family history are the most significant risk factors for the development of breast cancer. Other established risk factors include obesity, nulliparity and late age at first full-term pregnancy. The identified groups of women that may be at increased risk of developing breast cancer before menopause are long-term users of oral contraceptives (more than eight years) and starters at early age. In a few women, the use of oral contraceptives may accelerate the growth of an existing but undiagnosed breast cancer.

Women receiving oral contraceptives should be instructed in self-examination of their breasts. Their physicians should be notified whenever any masses are detected. A yearly clinical breast examination is also recommended because, if a breast cancer should develop, estrogen containing drugs may cause a rapid progression.

## **Cervical Cancer**

The most important risk factor for cervical cancer is persistent human papilloma virus (HPV) infection. Some epidemiological studies have indicated that long-term use of COCs containing ethinyl estradiol (>5 years) may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to the confounding effects, e.g. cervical screening and sexual behaviour. No epidemiological data on the risk of cervical cancer in users of NEXTSTELLIS are available.

## **Liver Tumors**

Women who have a history of or actual benign or malignant liver tumours should not use NEXTSTELLIS (see CONTRAINDICATIONS).

Hepatocellular carcinoma may be associated with oral contraceptives. The risk appears to increase with duration of hormonal contraceptive use. However, the attributable risk (the excess incidence) of liver cancers in oral contraceptive users is extremely small. A liver tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in women taking COCs.

## **Cardiovascular**

Epidemiological studies have suggested an association between the use of COCs and an increased risk of venous and arterial thrombotic and thromboembolic diseases such as deep venous thrombosis, pulmonary embolism, myocardial infarction, and of cerebrovascular accidents. These events occur rarely.

## **Venus thromboembolism (VTE)**

The use of any combined oral contraceptive (COC) carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive or restarts the same or a different COC. Data from a large, prospective 3-armed cohort study with EE-containing COCs suggest that this increased risk is mainly present during the first 3 months. VTE is life-threatening and is fatal in 1% to 2% of cases.

Overall, the risk for VTE in users of oral contraceptives with low estrogen content (<50 mcg ethinyl estradiol) is 2- to 3-fold higher than for nonusers of COCs who are not pregnant and remains lower than the risk associated with pregnancy and delivery. In women who do not use a COC and are not pregnant, about 1-5 out of 10,000 will develop a VTE over the period of one year, however this risk is approximately doubled with a range of 3-9 out of 10,000 woman-years for COC users. The rates of VTE are greater during pregnancy (usually 5-20 per 10,000 women-years), and it is especially high in women who are in the first 12 weeks of postpartum period (range from 40 to 65 per 10,000 woman-years).

Based on currently available information, DRSP-containing COCs with ethinyl estradiol (EE) may be associated with a higher risk of VTE than COCs containing the progestin levonorgestrel or some other progestins. Epidemiologic studies that compared the risk of VTE reported that the risk ranged from no increase to a three-fold increase. However, it is not yet known how the

risk of VTE with NEXTSTELLIS (a combination of Estetrol monohydrate and Drospirenone) compares with the risk with low dose levonorgestrel-containing COCs.

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.

### Symptoms of VTE (deep vein thrombosis)

VTE, manifesting as deep venous thrombosis (DVT) and/or pulmonary embolism (PE), may occur during the use of all COCs. Extremely rarely, thrombosis has been reported to occur in other blood vessels (e.g. hepatic, mesenteric, renal, cerebral, or retinal veins and arteries) in COC users.

In the event of symptoms, women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a COC.

Symptoms of deep vein thrombosis (DVT) can include:

- unilateral swelling of the leg and/or foot or along a vein in the leg;
- pain or tenderness in the leg which may be felt only when standing or walking;
- increased warmth in the affected leg; red or discoloured skin on the leg.

Symptoms of pulmonary embolism (PE) can include:

- sudden onset of unexplained shortness of breath or rapid breathing;
- sudden coughing which may bring up blood;
- sharp chest pain which may increase with deep breathing;
- sense of anxiety;
- severe light headedness or dizziness;
- rapid or irregular heartbeat.

Some of these symptoms (e.g. “shortness of breath”, “coughing”) are nonspecific and might be misinterpreted as more common or less severe events (eg, respiratory tract infections).

Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity (see Warnings and Precautions - Ophthalmologic).

### **Arterial thromboembolism (ATE)**

Epidemiological studies have associated the use of COCs with an increased risk for arterial thromboembolism (myocardial infarction) or for cerebrovascular accident (e.g., transient ischaemic attack, stroke). Arterial thromboembolic events may be fatal.

The risk for arterial thromboembolism (ATE) in users of oral contraceptives with low estrogen content (<50 mcg ethinyl estradiol) ranges from about 1 to 3 cases per 10,000 woman-years.

### Symptoms of ATE

Symptoms of a cerebrovascular event can include:

- sudden numbness or weakness of the face, arm or leg, especially on one side of the body;
- sudden trouble walking, dizziness, loss of balance or coordination;
- sudden confusion, trouble speaking or understanding;

- sudden trouble seeing in one or both eyes;
- sudden, severe or prolonged headache with no known cause;
- loss of consciousness or fainting with or without seizure.

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

Symptoms of myocardial infarction (MI) can include:

- pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone;
- discomfort radiating to the back, jaw, throat, arm, stomach;
- feeling of being full, having indigestion or choking;
- sweating, nausea, vomiting or dizziness;
- extreme weakness, anxiety, or shortness of breath;
- rapid or irregular heartbeats.

Historical or current symptoms of arterial thromboembolism may increase the risk of myocardial infarction or angina pectoris. If any of these symptoms is present, discontinuation of COCs and evaluation of the cause is recommended (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

### Important factors that increase the risk of VTE and ATE

The risk for venous thromboembolic complications and the risk of arterial thromboembolic complications or of a cerebrovascular event in COC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see Table 2)

NEXTSTELLIS is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis and arterial thrombosis (see CONTRAINDICATIONS). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk should be considered.

**Table 2: Risk factors for VTE and ATE**

<b>Risk factors</b>	<b>Comment</b>
Smoking, particularly in women over 35 years of age.	Women should be advised not to smoke if they wish to use a COC. Women over 35 who continue to smoke should NOT use any COC including NEXTSTELLIS.
Increasing age, particularly above 50 years.	No efficacy and safety data of NEXTSTELLIS are available in women over 50 years of age.
Obesity.	Risk increases substantially as BMI rises (>30 kg/m <sup>2</sup> ). Particularly important to consider if other risk factors also present.
Prolonged immobilization, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma.	In these situations, it is advisable to discontinue use of the pill (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilization. Another method

Risk factors	Comment
Note: temporary immobilization including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors.	of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if NEXTSTELLIS has not been discontinued in advance.
Positive family history (venous or arterial thromboembolism ever in a sibling or parent especially at a relatively early age, e.g., before 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use.  Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).
Other medical conditions associated with VTE.	Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.
Other medical conditions associated with adverse vascular events.	Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus.
Hypertension.	If sustained clinically significant hypertension develops during the use of a COC, it is prudent for the physician to suspend the intake of the tablets and treat the hypertension.
Migraine.	An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation.

## Hypertension

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. A relationship between COC use and clinical hypertension has not been established. However, if sustained clinically significant hypertension develops during the use of a COC, then it is prudent for the physician to suspend the intake of the tablets and treat the hypertension.

## **Driving and Operating Machinery**

No studies on the effects of NEXTSTELLIS on the ability to drive or use machines have been performed

## **Endocrine and Metabolism**

### **Diabetes**

Current low-dose oral contraceptives exert minimal impact on glucose metabolism. Diabetic patients, or those with a family history of diabetes, should be observed closely to detect any worsening of carbohydrate metabolism. Patients predisposed to diabetes who can be kept under close supervision may be given oral contraceptives. Young diabetic patients whose disease is of recent origin, well-controlled, and not associated with hypertension or other signs of vascular disease such as ocular fundal changes, should be monitored more frequently while using oral contraceptives.

### **Lipid and Other Metabolic Effects**

A small proportion of women will have adverse lipid changes while on oral contraceptives. Alternative contraception should be used in women with severe dyslipoproteinemia (see also **CONTRAINDICATIONS**). Elevations of plasma triglycerides may lead to pancreatitis and other complications.

## **Gastrointestinal**

Worsening of Crohn's disease and ulcerative colitis has been reported during COC use.

The efficacy of COCs may be reduced in the event of missed tablets (see DOSAGE AND ADMINISTRATION, gastro-intestinal disturbances during active tablet taking (see DOSAGE AND ADMINISTRATION) or concomitant medication (see DRUG INTERACTIONS).

## **Genitourinary**

### **Vaginal Bleeding**

Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology. See also WARNINGS AND PRECAUTIONS section: Sexual Function/Reproduction.

### **Fibroids**

Patients with fibroids (leiomyomata) should be carefully observed. Sudden enlargement, pain, or tenderness requires discontinuation of the use of oral contraceptives.

## **Hepatic/Biliary/Pancreatic**

NEXTSTELLIS is contraindicated in patients with active liver disease or abnormal liver function testing (see CONTRAINDICATIONS).

## **Hepatic Function**

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal.

## **Jaundice**

Discontinue NEXTSTELLIS if jaundice develops.

Oral contraceptive-related cholestasis may occur in women with a history of pregnancy-related cholestasis. Women with a history of COC-related cholestasis may have the condition recur with subsequent COC use.

## **Hepatitis C**

Caution is warranted when starting therapy with the Hepatitis C virus (HCV) combination drug regimen ombitasvir, paritaprevir, ritonavir, with or without dasabuvir (see DRUG INTERACTIONS).

During clinical trials with patients treated for hepatitis C virus infection (HCV) with medicinal products containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, alanine transaminase (ALT) elevations higher than 5 times the upper limit of normal occurred significantly more frequent in women using ethinyl estradiol containing medications such as COC. See section OTHER DRUG-DRUG INTERACTIONS.

## **Gallbladder Disease**

Patients taking oral contraceptives have a greater risk of developing gallbladder disease requiring surgery within the first year of use. The risk may double after four or five years.

## **Immune**

### **Angioedema**

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

## **Monitoring and Laboratory Tests**

### **Physical Examination and Follow-up**

Before oral contraceptives are used, a thorough history and physical examination should be performed, including a blood pressure determination and the family case history carefully noted. In addition, disturbances of the clotting system must be ruled out if any members of the family have suffered from thromboembolic diseases (e.g., deep vein thrombosis, stroke, myocardial infarction) at a young age. Breasts, liver, extremities, and pelvic organs should be examined and a Papanicolaou (PAP) smear should be taken if the patient has been sexually active.

The first follow-up visit should be done 3 months after oral contraceptives are prescribed. Thereafter, examinations should be performed at least once a year, or more frequently if



indicated. At each annual visit, examination should include those procedures that were done at the initial visit as outlined above or per recommendations of the Canadian Task Force on the Periodic Health Examination.

Consider monitoring serum potassium concentration in high-risk patients who take a strong CYP3A4 inhibitor long-term and concomitantly.

## **Neurologic**

### **Migraine and Headache**

The onset or exacerbation of migraine or the development of headache of a new pattern that is recurrent, persistent or severe, requires discontinuation of COCs and evaluation of the cause (see CONTRAINDICATIONS).

## **Ophthalmologic**

With use of COCs, there have been reports of retinal vascular thrombosis which may lead to partial or complete loss of vision. If there are signs or symptoms such as visual changes, onset of proptosis or diplopia, papilledema, or retinal vascular lesions, NEXTSTELLIS should be discontinued and the cause immediately evaluated.

Sometimes loss of vision can occur almost immediately.

## **Peri-Operative Considerations**

There is an increased risk of thromboembolic complications in COC users after major surgery. If feasible, COCs should be discontinued and an alternative method substituted at least one month prior to major elective surgery and during periods of prolonged immobilization. COC use should not be resumed for at least two weeks after major elective surgery (See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS - Cardiovascular).

## **Psychiatric**

### **Depression**

Patients with a history of emotional disturbances, especially the depressive type, may be more prone to have a recurrence of depression while taking oral contraceptives. In cases of a serious recurrence, a trial of an alternate method of contraception should be made which may help to clarify the possible relationship. Women with premenstrual syndrome (PMS) may have a varied response to oral contraceptives, ranging from symptomatic improvement to worsening of the condition.

## **Renal**

### **Fluid Retention**

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

## **Sexual/Reproductive Health**

### **Return to Fertility**

NEXTSTELLIS is indicated for oral contraception. After discontinuing oral contraceptive therapy, the patient may delay pregnancy until at least one normal spontaneous cycle has occurred in order to date the pregnancy. An alternate contraceptive method should be used during this time.

### **Bleeding Irregularities**

With all COCs, irregular spotting or bleeding may occur, especially during the first months of use. For women using NEXTSTELLIS, most of these episodes concerned spotting only.

If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy.

Based on patient diaries from two pivotal clinical trials of NEXTSTELLIS, after the first cycle, 14% to 21% of women experienced unscheduled bleeding or spotting per 28-day cycle, and about 87% to 90% of women using NEXTSTELLIS experienced scheduled withdrawal bleeding/spotting.

In some women (10-13%), withdrawal bleeding may not occur during the inert tablet phase. If absence of withdrawal bleeding occurs and NEXTSTELLIS has been taken according to the instructions as described in Dosage and Administration section, pregnancy is unlikely. If NEXTSTELLIS has not been taken as directed, or if two consecutive withdrawal bleeds do not occur, pregnancy must be ruled out before NEXSTELLIS use can be continued.

### **Skin**

Chloasma may occasionally occur in women who take COCs, 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 COCs.

## **7.1 Special Populations**

### **7.1.1 Pregnant Women**

NEXTSTELLIS is not indicated during pregnancy.

If pregnancy occurs while taking NEXTSTELLIS, further intake must be stopped.

Animal studies have shown undesirable effects during pregnancy and lactation (see ACTION AND CLINICAL PHARMACOLOGY). Based on these animal data, undesirable effects due to hormonal action of the active compounds cannot be excluded. Clinical data is limited to draw any conclusions regarding safety of NEXTSTELLIS during pregnancy.

The increased risk of VTE during the postpartum period should be considered when re-starting NEXTSTELLIS (see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

### 7.1.2 Breast-feeding

Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the breast milk. Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Therefore, the use of COCs should not be recommended until the breast-feeding mother has completely weaned her child and an alternative contraceptive method should be advised to women wishing to breastfeed.

### 7.1.3 Pediatrics

**Pediatrics (< 16 years of age):** No data are available to Health Canada. Therefore, Health Canada has not authorized an indication for pediatric use. Use of this product before menarche is not indicated.

### 7.1.4 Geriatrics

**Geriatrics:** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for women over 50 years of age. NEXTSTELLIS is not indicated after menopause.

### 7.1.5 Body Mass Index (BMI)

The safety and efficacy of NEXTSTELLIS in women with a body mass index (BMI) > 35 kg/m<sup>2</sup> has not been evaluated.

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

An increased risk of the following serious adverse reactions has been observed in women using COCs (see WARNINGS AND PRECAUTIONS):

- arterial thromboembolism;
- myocardial infarction;
- pulmonary embolism;
- stroke;
- transient ischemic attacks;
- venous thrombosis;
- liver disease.

The most commonly reported adverse reactions related to NEXTSTELLIS are metrorrhagia, menorrhagia, dysmenorrhoea, headache, acne, and breast pain/tenderness.

### 8.2 Clinical Trial Adverse Reactions

*Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials therefore may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction*

information from clinical trials may be useful for identifying and approximating rates of adverse drug reactions in real-world use.

### **Adverse Drug Reactions**

To assess the safety of NEXTSTELLIS for the proposed indication, data were pooled from two Phase 3 (C301 and C302) and three Phase 2 (C201, C202 and ES-C02) studies. These studies were conducted in healthy pre-menopausal women between 16-50 years of age with a duration of study at least three 28-day cycles, and included the dosage and regimen of NEXTSTELLIS (E4/DRSP 15/3 mg, 24/4). The safety analysis included safety data from 3,790 subjects, of which a total of 3,575 subjects was confirmed treated. A total of 2,212 subjects completed 13 cycles of treatment in the two Phase 3 studies. Treated subjects contributed a total of 2,735 woman-years (WY) or 35,677 cycles of exposure. Within the treated population, 3,181 women aged 16 to 35 years contributed 31,412 cycles, while 394 women aged 36 to 50 years contributed 4,266 cycles. The safety population (n=3,790) also included 215 subjects who were dispensed study medication, but for whom the actual intake of study medication was not confirmed.

Approximately 50% of the subjects reported a Treatment-Emergent Adverse Event (TEAE), of which approximately half was judged to be related to NEXTSTELLIS. Less than 10% of TEAEs resulted in premature discontinuation.

The most frequently reported adverse reactions ( $\geq 1\%$ ) were metrorrhagia (4.3%), headache (3.2%), acne (3.2%), vaginal hemorrhage (2.7%), dysmenorrhea (2.4%), breast pain (2.1%), weight increased (2.0%), breast pain/tenderness (1.8%), libido decreased (1.5%), nausea (1.4%), menorrhagia (1.3%) and mood swings (1.3%).

In subjects aged  $\geq 16$  to  $\leq 35$  years, relative distributions of TEAEs were similar to that observed in the all-subjects population.

Table 3 below presents the treatment-emergent adverse events (TEAE) that occurred in at least 1% of the subjects from the safety analysis, and suspected to have a causal relationship to NEXTSTELLIS.

**Table 3: Related TEAEs Experienced by  $\geq 1\%$  of the Subjects by System Organ Class and Preferred Term (Safety Population)**

System Organ Class Preferred Term	PHASE 2 and 3 STUDIES 15 mg estetrol monohydrate /3 mg drospirenone (N=3,790)	
	n	%
<b>Any Treatment-Emergent Adverse Events</b>	<b>1056</b>	<b>20.9</b>
<b>Reproductive system and breast disorders</b>	<b>599</b>	<b>15.8</b>
Metrorrhagia	162	4.3
Vaginal haemorrhage	103	2.7
Dysmenorrhoea	92	2.4
Breast pain	79	2.1
Breast tenderness	67	1.8
Menorrhagia	51	1.3
<b>Gastrointestinal disorders</b>	<b>138</b>	<b>3.6</b>

System Organ Class Preferred Term	PHASE 2 and 3 STUDIES 15 mg estetrol monohydrate /3 mg drospirenone (N=3,790)	
	n	%
Nausea	52	1.4
<b>Psychiatric disorders</b>	<b>211</b>	<b>5.6</b>
Libido decreased	56	1.5
Mood swings	50	1.3
<b>Nervous system disorders</b>	<b>170</b>	<b>4.5</b>
Headache	123	3.2
<b>Skin and subcutaneous tissue disorders</b>	<b>155</b>	<b>4.1</b>
Acne	122	3.2
<b>Investigations</b>	<b>122</b>	<b>3.2</b>
Weight increased	75	2.0
<b>General disorders and administration site conditions</b>	<b>51</b>	<b>1.3</b>

n = number of subjects; TEAE = Treatment Emergent Adverse Event.

A total of 45 serious TEAEs (all serious adverse events emerging during the studies without regards to the relationship to the drug) was reported by 41 subjects (1.1%) included in the safety population. These include 9 cases of spontaneous abortion, 2 cases of ectopic pregnancy, 7 cases of psychiatric disorders, 2 cases of depression, and one case of vascular disorder and one case of venous thrombosis.

### **Discontinuations due to Adverse Events**

Medical reasons for discontinuation (n=398, 10.5%) included TEAEs (N=356, 9.4%) and can be divided into TEAEs not related to vaginal bleeding (n=250, 6.6%) and related to vaginal bleeding (n=106, 2.8%). Other medical reasons included pregnancy (n=41, 1.1%) and death (n=1, 0.03%).

The system organ classes containing most TEAEs leading to discontinuations ( $\geq 1\%$ ) were reproductive system and breast disorders (3.6%), psychiatric disorders (2.7%) and skin and subcutaneous tissue disorders (1.2%). Individual events leading to discontinuation, mentioned with a frequency of 0.2% (equivalent to 6 subjects) or more, included in order of frequency metrorrhagia (1.1%), acne (0.9%), vaginal hemorrhage (0.7%), menorrhagia (0.6%), libido decreased (0.5%), mood swings (0.5%), weight increased (0.4%), mood altered (0.4%), headache (0.4%), depression (0.2%), irritability (0.2%), breast pain (0.2%), anxiety (0.2%), menstruation irregular (0.2%), dysmenorrhea (0.2%), abdominal pain (0.2%), migraine with aura (0.2%), migraine (0.2%) and nausea (0.2%).

### **8.3 Less Common Clinical Trial Adverse Reactions (< 1%)**

**Ear and labyrinth disorders:** Vertigo

**Eye disorders:** Dry eye, Vision blurred, Visual impairment

**Gastrointestinal disorders:** Abdominal distension, Colitis, Constipation, Diarrhoea, Dry mouth, Dyspepsia, Flatulence, Gastrointestinal motility disorder, Gastro-oesophageal reflux disease, Lip swelling, Vomiting

**General disorders and administration site conditions:** Abdominal pain, Chest pain, Fatigue, Feeling abnormal, Hyperthermia, Malaise<sup>(1)</sup>, Oedema, Pain

**Immune system disorders:** Hypersensitivity

**Infections and infestations:** Bacterial vaginosis, Candida infection, Cystitis, Fungal infection, Genital infection fungal, Mastitis, Urinary tract infection, Vaginal infection, Vulvovaginal candidiasis, Vulvovaginal mycotic infection

**Injury, poisoning and procedural complications:** Contusion, Procedural headache

**Investigations:** Abnormal renal function test, Blood in urine, Decreased haemoglobin, Decreased serum ferritin, Increased blood glucose, Increased blood potassium, Increased blood pressure, Increased hepatic enzyme

**Metabolism and nutrition disorders:** Appetite disorder, Fluid retention, Hyperkalaemia

**Musculoskeletal and connective tissue disorders:** Back pain, Joint swelling, Limb discomfort, Muscle spasms, Pain in extremity

**Neoplasms benign, malignant and unspecified (incl cysts and polyps):** Fibroadenoma of breast

**Nervous system disorders:** Amnesia, Dizziness, Migraine, Paraesthesia, Somnolence

**Pregnancy, puerperium and perinatal conditions:** Ectopic pregnancy

**Psychiatric disorders:** Anxiety disorder<sup>(2)</sup>, Depression<sup>(3)</sup>, Emotional disorder<sup>(4)</sup>, Insomnia, Nervousness, Stress

**Renal and urinary disorders:** Abnormal urine odour, Bladder spasm

**Reproductive system and breast disorders:** Abnormal withdrawal bleeding<sup>(5)</sup>, Breast discolouration, Breast mass<sup>(6)</sup>, Breast swelling, Coital bleeding, Dysfunctional uterine bleeding, Dyspareunia, Endometrial disorder, Lactation disorders, Menometrorrhagia, Nipple disorder, Ovarian cyst, Pelvic pain, Premenstrual syndrome, Uterine haemorrhage, Uterine spasm, Vaginal discharge, Vulvovaginal disorder<sup>(7)</sup>

**Respiratory, thoracic and mediastinal disorders:** Asthma, Dyspnoea

**Skin and subcutaneous tissue disorders:** Alopecia, Dermatitis<sup>(8)</sup>, Hirsutism, Hyperhidrosis<sup>(9)</sup>, Pigmentation disorder<sup>(10)</sup>, Pruritus, Seborrhoea, Skin discolouration, Skin disorders<sup>(11)</sup>, Swelling of face, Urticaria

**Vascular disorders:** Hot flush, Hypertension, Hypotension, Thrombophlebitis, Venous thrombosis, Varicose vein

- (1) including Malaise and Decreased performance status
- (2) including Agitation, Anxiety, Generalised anxiety disorder and Panic attack
- (3) including Depressed mood, Depressive symptom, Tearfulness and Depression
- (4) including Emotional disorder, Emotional distress and Crying
- (5) including Abnormal withdrawal bleeding, Amenorrhoea, Menstrual disorder, Irregular menstruation, Oligomenorrhoea and Polymenorrhoe
- (6) including Breast mass and Fibrocystic breast disease
- (7) including Vaginal odour, Vulvovaginal discomfort, Vulvovaginal dryness, Vulvovaginal pain, Vulvovaginal pruritus and Vulvovaginal burning sensation
- (8) including Dermatitis and Eczema
- (9) including Night sweats, Hyperhidrosis and Cold sweat
- (10) including Chloasma and Skin hyperpigmentation
- (11) including Dry skin, Rash and Skin swelling

## 8.4 Clinical Trial Adverse Reactions (Pediatrics < 16 years of age)

The safety and efficacy of NEXTSTELLIS have not been studied in the pediatric population.

## 9 DRUG INTERACTIONS

### 9.1 Overview

The concurrent administration of oral contraceptives with other medicines may lead to breakthrough bleeding and/or may result in an altered response to either agent. It is important to ascertain all drugs that a patient is taking, both prescription and non-prescription, before oral contraceptives are prescribed.

#### *In vitro assessment of interactions*

*In vitro* metabolism studies indicated that estetrol does not inhibit the major CYP450 isoforms. E4 showed low inhibitory properties towards human UGT1A9 and UGT2B7. At the clinical dose, interaction of estetrol with the metabolism of other drugs by UGT1A9 and UGT2B7 is not expected.

Transporters OATP1B1, OATP1B3, OAT1, OCT2, MATE1 and MATE2-K did not play a role in the cellular uptake of E4. While it cannot be entirely excluded that E4 acts as a substrate for OAT3, the importance of OAT3 in the cellular uptake of E4 interaction, is considered to be low and the risk of a potential drug interaction with other drugs affecting the OAT3 transporter is expected to be limited.

E4 is a medium to high permeability compound and acts as a potential substrate for both efflux ABC transporters P-gp and BCRP. As P-gp and BCRP are not expected to impact the oral bioavailability of highly permeable and highly soluble drugs the intestinal absorption of E4 is not expected to be significantly affected by BCRP-mediated efflux.

*In vitro* metabolism studies indicated that DRSP is capable to inhibit weakly to moderately the CYP450 enzymes CYP2C9, CYP2C19 and CYP3A4. DRSP is also subject to oxidative metabolism catalyzed by CYP3A4 (see section DRUG-DRUG INTERACTIONS).

### 9.2 Drug-Drug Interactions

Interactions of NEXTSTELLIS can occur with drugs that induce microsomal enzymes which can result in increased clearance of sex hormones, and which may lead to breakthrough bleeding and/or contraceptive failure. Enzyme induction can already be observed after a few days of treatment. Maximum enzyme induction is generally seen within a few weeks. After the cessation of drug therapy, enzyme induction may be sustained for about 4 weeks.

Several of the anti-HIV/HCV protease inhibitors (e.g., ritonavir, telaprevir, boceprevir) and nonnucleoside reverse transcriptase inhibitors (e.g., nevirapine) have been studied with coadministration of oral combination hormonal contraceptives; significant changes (increase or decrease) in the mean AUC of the estrogen or progestogen have been noted in some cases. The efficacy and safety of oral contraceptive products may be affected. Healthcare providers should refer to the label of the individual anti-HIV/HCV protease inhibitor for further drug-drug interaction information.

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g., ketoconazole, itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g., clarithromycin, erythromycin), diltiazem and grapefruit juice, can increase plasma concentrations of the progestin. Increase in DRSP may increase serum potassium levels, possibly increasing the risk of hyperkalemia in high-risk patients (see WARNINGS AND PRECAUTIONS, General).

**Table 4: Drugs which may decrease the efficacy of oral contraceptives**

Class of Compound	Drug	Proposed mechanism	Suggested Management
Antacids		Decreased intestinal absorption of progestins.	Dose 2 hours apart.
Antibiotics	Ampicillin Cotrimoxazole Penicillin	Enterohepatic circulation disturbance, intestinal hurry.	For short course, use additional non-hormonal method of contraception or use another drug. For long course, use another non-hormonal method of contraception.
	Rifabutin Rifampin	Increased metabolism of progestins. Suspected acceleration of estrogen metabolism.	Use another non-hormonal method of contraception.
	Chloramphenicol Metronidazole Neomycin Nitrofurantoin Sulfonamides Tetracyclines	Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation.	For short course, use additional non-hormonal method of contraception or use another drug. For long course, use another non-hormonal method of contraception.
	Troleandomycin	May retard metabolism of oral contraceptives, increasing the risk of cholestatic jaundice.	
Anticonvulsants	Carbamazepine Ethosuximide Felbamate Lamotrigine Oxcarbazepine Phenobarbital Phenytoin Primidone Topiramate	Induction of hepatic microsomal enzymes. Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG.	Use higher dose oral contraceptives (50 µg ethinyl estradiol), another drug or another non-hormonal method of contraception.
Antifungals	Griseofulvin	Stimulation of hepatic metabolism of contraceptive steroids may occur.	Use another non-hormonal method of contraception.
Cholesterol Lowering Agents	Clofibrate	Reduces elevated serum triglycerides and cholesterol; this reduces oral contraceptive efficacy.	Use another non-hormonal method of contraception.
HCV Protease Inhibitors	Boceprevir Telaprevir	Remains to be confirmed.	Use another drug or another non-hormonal



			method of contraception.
HIV Protease Inhibitors	Ritonavir	Induction of hepatic microsomal enzymes.	Use another drug or another non-hormonal method of contraception.
Non-nucleoside reverse transcriptase inhibitors	Nevirapine	Induction of hepatic microsomal enzymes.	Use another drug or another non-hormonal method of contraception.
Sedatives and Hypnotics	Barbiturates Benzodiazepines Chloral hydrate Glutethimide Meprobamate	Induction of hepatic microsomal enzymes.	For short course, use additional non-hormonal method of contraception or another drug. For long course, use another non-hormonal method of contraception or higher dose oral contraceptives.
Other Drugs	Analgesics Antihistamines Antimigraine preparations Phenylbutazone preparations Vitamin E	Reduced oral contraceptive efficacy has been reported. Remains to be confirmed.	

In a study with NEXTSTELLIS, co-administration of the strong UGT2B7 inhibitor valproic acid for 12 days increased the peak and overall exposure to estetrol 1.36 and 1.13 fold, respectively, and did not impact drospirenone. These changes are considered of no clinical relevance.

**Table 5: Modification of other drug action by oral contraceptives**

<b>Class of Compound</b>	<b>Drug</b>	<b>Modification of Drug Action</b>	<b>Suggested Management</b>
Alcohol		Possible increased levels of ethanol or acetaldehyde.	Use with caution.
Alpha-II adrenoreceptor agents	Clonidine	Sedation effect increased.	Use with caution.
Anticoagulants	All	Oral contraceptives increase clotting factors, decrease efficacy. However, oral contraceptives may potentiate action in some patients.	Use another non-hormonal method of contraception.
Anticonvulsants	All	Estrogens may increase risk of seizures.	Use another non-hormonal method of contraception.
	Lamotrigine	Decreased lamotrigine levels, may lead to	Use another non-hormonal method of contraception.

		breakthrough seizures.	
Antidiabetic drugs	Oral hypoglycemics and insulin	Oral contraceptives may impair glucose tolerance and increase blood glucose.	Use low-dose estrogen and progestin oral contraceptive or another non-hormonal method of contraception. Monitor blood glucose.
Antihypertensive agents	Guanethidine and methyldopa	Estrogen component causes sodium retention, but effect of E4 is not yet known. Progestin has no effect.	Use low-dose estrogen oral contraceptive or use another nonhormonal method of contraception.
	Beta blockers	Increased drug effect (decreased metabolism).	Adjust dose of drug if necessary. Monitor cardiovascular status.
Antipyretics	Acetaminophen	Increased metabolism and renal clearance.	Dose of drug may have to be increased.
	Antipyrine	Impaired metabolism.	Decrease dose of drug.
	ASA	Effects of ASA may be decreased by the short-term use of oral contraceptives.	Patients on chronic ASA therapy may require an increase in ASA dosage.
Betamimetic agents	Isoproterenol	Estrogen causes decreased response to these drugs.	Adjust dose of drug as necessary. Discontinuing oral contraceptives can result in excessive drug activity.
Caffeine		The actions of caffeine may be enhanced as oral contraceptives may impair the hepatic metabolism of caffeine.	Use with caution.
Cholesterol lowering agents	Clofibrate	Their action may be antagonized by oral contraceptives containing DRSP. DRSP may also increase metabolism of clofibrate.	May need to increase dose of clofibrate.
Corticosteroids	Prednisone	Markedly increased serum levels.	Possible need for decrease in dose.
Cyclosporine		May lead to an increase in cyclosporine levels and hepatotoxicity.	Monitor hepatic function. The cyclosporine dose may have to be decreased.
Direct-acting antiviral (DAA) medicinal products	Ombitasvir, Paritaprevir, Ritonavir, with and without Dasabuvir	Has been shown to be associated with increases in ALT levels 5 to > 20 times the upper limit of normal in healthy female subjects and HCV infected women	See <b>WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic</b>

Folic acid		Oral contraceptives have been reported to impair folate metabolism.	May need to increase dietary intake, or supplement.
Meperidine		Possible increased analgesia and CNS depression due to decreased metabolism of meperidine.	Use combination with caution.
Phenothiazine tranquilizers	All phenothiazines, reserpine and similar drugs	Estrogen potentiates the hyperprolactinemia effect of these drugs, but the effect of E4 is not yet known.	Use other drugs . If galactorrhea or hyperprolactinemia occurs, use other non-hormonal method of contraception.
Sedatives and hypnotics	Chlordiazepoxide Diazepam Lorazepam Oxazepam	Increased effect (increased metabolism).	Use with caution.
Theophylline	All	Decreased oxidation, leading to possible toxicity.	Use with caution. Monitor theophylline levels.
Tricyclic antidepressants	Clomipramine (possibly others)	Increased side effects: eg, depression.	Use with caution.
Vitamin B12		Oral contraceptives have been reported to reduce serum levels of Vitamin B12.	May need to increase dietary intake, or supplement.

### ***Interactions With Drugs That Have the Potential to Increase Serum Potassium***

In patients without renal insufficiency, the concomitant use of drospirenone and ACE-inhibitors or NSAIDs did not show a significant effect on serum potassium. Nevertheless, concomitant use of NEXTSTELLIS with aldosterone antagonists or potassium-sparing diuretics has not been studied. In this case, serum potassium should be tested during the first treatment cycle. See Warnings and Precautions.

During clinical trials with patients treated for hepatitis C virus infection (HCV) with medicinal products containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, alanine transaminase (ALT) elevations higher than 5 times the upper limit of normal occurred significantly more frequent in women using ethinylestradiol containing medications such as CHCs. Women using medications containing estrogens other than ethinylestradiol had a rate of ALT elevation similar to those not receiving any estrogens; however, due to the limited number of women taking these other estrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir.

### **9.3 Drug-Food Interactions**

There is no clinically relevant interaction of either estetrol or drospirenone with food intake.

## 9.4 Drug-Herb Interactions

Herbal products containing St. John's Wort (*Hypericum perforatum*) may induce hepatic enzymes (cytochrome P450) and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

## 9.5 Drug-Laboratory Test Interactions

Results of laboratory tests should be interpreted with the knowledge that the patient is taking an oral contraceptive. The following laboratory tests are modified:

### ***Liver Function Tests***

Aspartate serum transaminase (AST) - variously reported elevations.

Alkaline phosphatase and gamma glutamine transaminase (GGT) - slightly elevated.

### ***Coagulation Tests***

Minimal elevation of test values reported for such parameters as prothrombin and factors VII, VIII, IX, and X.

### ***Thyroid Function Tests***

Protein binding of thyroxine is increased as indicated by increased total serum thyroxine concentrations and decreased T3 resin uptake.

### ***Lipoproteins***

Small changes of unproven clinical significance may occur in lipoprotein cholesterol fractions.

### ***Gonadotropins***

LH and FSH levels are suppressed by the use of oral contraceptives. Wait 2 weeks after discontinuing the use of oral contraceptives before measurements are made.

### ***Glucose Tolerance***

Oral glucose tolerance remained unchanged or was slightly decreased.

### ***Tissue Specimens***

Pathologists should be advised of oral contraceptive therapy when specimens obtained from surgical procedures and PAP smears are submitted for examination.

## 9.6 Drug-Lifestyle Interactions

See **Serious Warnings and Precautions** about cigarette smoking.

No studies on the effects of NEXTSTELLIS on the ability to drive or use machines have been performed.

## 10 ACTION AND CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

NEXTSTELLIS is a monophasic, combination oral contraceptive that contains the progestin drospirenone (3.0 mg) and the estrogen estetrol monohydrate (15 mg). Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this

action is inhibition of ovulation, combinations of estrogens and progestins also produce a change in the cervical mucus, in the uterine endometrium, and in motility and secretion in the uterine tube.

Drospirenone is a spironolactone analogue with antiminerlocorticoid activity. Preclinical studies in animals and *in vitro* have shown that drospirenone has no androgenic, estrogenic, glucocorticoid, and antiglucocorticoid activity. Preclinical studies in animals have also shown that drospirenone has antiandrogenic activity.

E4 is a naturally occurring estrogen produced by the human fetal liver. The E4 in NEXTSTELLIS is synthesized from a plant source. It is only produced during human pregnancy and reaches the maternal circulation through the placenta. E4 displays a high selectivity for estrogen receptors (ERs) and binds to both ER $\alpha$  and ER $\beta$ , with a 4 to 5 times higher affinity for ER $\alpha$  compared to ER $\beta$ . Estrogenic properties of E4 were confirmed in several *in vivo* PD models. It acts as an estrogen agonist on the vagina, the uterus and the endometrium, the bones and the brain, and as an antagonist in breast tissues. E4 differs from ethinylestradiol by the lack of an ethinyl group in the 17-alpha position. In humans, E4 is an end-product of steroid metabolism and is not reconverted to estriol (E3), estradiol (E2) or estrone (E1).

E4 as monotherapy suppresses ovarian activity and inhibits ovulation dose-dependently. However, complete ovarian suppression is only obtained when E4 is combined with a progestin.

### Non-contraceptive Benefits of Combination Oral Contraceptives

Several health advantages other than contraception have been reported for COCs:

1. Combination oral contraceptives reduce the incidence of cancer of the endometrium and ovaries.
2. Oral contraceptives reduce the likelihood of developing benign breast disease and, as a result, decrease the incidence of breast biopsies.
3. Oral contraceptives reduce the likelihood of development of functional ovarian cysts.
4. Pill users have less menstrual blood loss and have more regular cycles, thereby reducing the chance of developing iron-deficiency anemia.
5. The use of oral contraceptives may decrease the severity of dysmenorrhea and premenstrual syndrome, and may improve acne vulgaris, hirsutism, and other androgen-mediated disorders.
6. Oral contraceptives decrease the incidence of acute pelvic inflammatory disease and, thereby, reduce as well the incidence of ectopic pregnancy.
7. Oral contraceptives have potential beneficial effects on endometriosis.

## **10.2 Pharmacodynamics**

### Dose response

The estrogen and progestin dose combination in NEXTSTELLIS was based on the provision of adequate ovulation inhibition and acceptable cycle control. COCs act primarily by providing ovulation inhibition, while the remaining ovarian activity determines the contraceptive robustness, i.e., the vulnerability to non-compliance, or to interacting conditions and drugs. Because control of vaginal bleeding is the major determinant of the tolerability of a COC, this is an important element of dose selection too.

Estetrol is dose-dependently associated with the suppression of ovarian activity. Estetrol alone in daily doses of up to 20 mg is not capable of consistently inhibiting ovulation, but estetrol adds to the extent of progestin-induced ovarian suppression and consequently contributes to the ovulation inhibition induced by a combination of estetrol and a progestin. All combinations containing estetrol monohydrate 5 mg or more with drospirenone 3 mg provide ovulation inhibition, but for adequate cycle control more than 10 mg of estetrol monohydrate is required. The optimum combination of estetrol and drospirenone is the one containing estetrol monohydrate/drospirenone 15/3 mg in a 24/4 regimen, which provides full ovulation inhibition and the most predictable vaginal bleeding pattern.

Study ES-C02 was a randomized, open-label, multicenter, dose-finding study designed to select the optimal combination of estetrol plus the progestin drospirenone or levonorgestrel for the Phase 3 clinical program, with a group using estradiol valerate/dienogest as reference therapy. Altogether 389 young, healthy female volunteers (mean age 24.1 years, range: 18-35 years) received one of five treatments for 6 treatment cycles of 28 days each. The primary endpoints of this study were to assess vaginal bleeding patterns (cycle control) by measuring the occurrence of unscheduled bleeding/spotting and absence of withdrawal bleeding. The results of this study showed that the incidence of subjects with unscheduled bleeding/spotting was generally lower in the E4/DRSP groups across the primary cycles than in the other treatment groups. By cycle 6, the 15 mg E4/DRSP group had the lowest incidence (33.8%) of unscheduled bleeding/spotting among all groups. An absence of withdrawal bleeding occurred in <20% of subjects in all E4 treatment groups. At cycle 6, the 15 mg E4/DRSP group had the lowest incidence (3.5%) of absence of withdrawal bleeding among all groups

#### Endocrine function, Metabolic and Hemostasis

Study 201 was a single-center, randomized, open-label, three-arm study to evaluate the effect of estetrol monohydrate (15 mg) in combination with drospirenone (3 mg) and of two reference COCs containing either ethinyl estradiol (30 mcg) and levonorgestrel (150 mcg) or ethinyl estradiol (20 mcg) and drospirenone (3 mg) on endocrine function, metabolic control and hemostasis during 6 treatment cycles. A total of 101 healthy female subjects were randomized, of these 98 subjects between 18 and 47 years of age and with a BMI between 18.3 and 30.0 kg/m<sup>2</sup>.

No clear changes between baseline and Cycle 6 were observed for endocrine parameters such as dehydroepiandrosterone sulfate (DHEAS), dihydrotestosterone (DHT), testosterone, prolactin, free triiodothyronine, free thyroxine and thyrotropin, and cortisol. Treatment with estetrol monohydrate (15 mg)/drospirenone (3 mg) did not result in an apparent decrease in follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels.

Treatment with estetrol monohydrate (15 mg)/drospirenone (3 mg) resulted in small increases from baseline to Cycle 6 with respect to liver protein such as angiotensinogen and CBG, SHBG, and TBG. There was no apparent change for C-reactive protein (CRP). Additionally, treatment with estetrol monohydrate (15 mg)/drospirenone (3 mg) resulted in little changes from baseline to Cycle 6 in lipid profile parameters such as cholesterol, HDL cholesterol, LDL cholesterol, lipoprotein-a, and triglycerides.

There were also no obviously changes from baseline to Cycle 6 with respect to glucose metabolism parameters such as insulin and glucose level.

In subjects treated with estetrol monohydrate/drospirenone 15/3 mg combination, no obvious changes from baseline to Cycle 6 were observed for hemostasis parameters such as fibrinogen, factor VIII Activity, von Willebrand factor, PAI-1, soluble E-selectin, prothrombin fragments 1+2, prothrombin activity (factor II), antithrombin, protein C activity (Factor XIV), TFPI, APC resistance (ETP) and D-dimer.

### Ovarian Function and Follicular Size

Study 202 was a single-center, randomized, open-label, two-arm study to evaluate the effects of estetrol monohydrate (15 mg)/drospirenone (3 mg) combination and the 20 mcg ethinyl estradiol (EE)/3 mg DRSP combination as reference on ovarian function inhibition at Treatment Cycle 1 and Treatment Cycle 3. A total of 82 female subjects between 19 and 35 years of age and with a BMI between 18.6 and 34.9 kg/m<sup>2</sup> participated in the study. The primary endpoint was Hoogland score at Treatment Cycle 1 and Treatment Cycle 3 based on follicular size assessed by transvaginal ultrasonography (TVUS) and endogenous hormone levels: serum E2 and serum progesterone. The results of study 202 showed that ovarian function inhibition was adequate in both treatment groups. The overall Hoogland scores for both treatments were similar in Treatment Cycle 1. However in Treatment Cycle 3, slightly higher percentage (20%) of subjects treated with estetrol monohydrate (15 mg)/drospirenone (3 mg) having a Hoogland score of 4 when compared with that (4.9%) treated with 20 mcg EE/3 mg DRSP.

### Cardiac Electrophysiology

In a randomized, double-blind, multiple-dose, parallel group, placebo- and positive-controlled ECG assessment study in healthy female subjects (N=32/treatment group), estetrol (E4) in combination with drospirenone (DRSP) administered as a therapeutic dose of 15 mg E4/3 mg DRSP from Day 1-10 followed by a suprathreshold dose of 75 mg E4/15 mg DRSP (5X multiple of therapeutic dose) from Day 11-20 was not observed to have any clinically relevant effects on the QTc interval.

## 10.3 Pharmacokinetics

**Table 6: Summary of Pharmacokinetic Parameters (Estetrol 15 mg / Drospirenone 3 mg) in healthy women**

	<b>C<sub>max</sub></b> (ng/mL) Geo mean (CV%)	<b>T<sub>max</sub></b> (h) Median (range)	<b>t<sub>1/2</sub></b> (h) Geo mean (CV%)	<b>AUC<sub>0-24</sub></b> (ng•h/mL) Geo mean (CV%)
<b>Single dose</b>				
<b>E4</b>	18.0 (47.1)	0.50 (0.50 – 2.00)	24.3 (37.7)	36.4 (27.7)
<b>DRSP</b>	32.4 (27.8)	1.50 (1.00 – 4.00)	32.9 (33.3)	224 (29.6)
<b>Multiple dose (Day 14)</b>				
<b>E4</b>	17.9 (75.2)	0.51 (0.50 – 2.00)	24.3 (26.3)	59.1 (23.5)
<b>DRSP</b>	48.7 (25.7)	1.00 (1.00 – 3.00)	34.2 (31.3)	519 (28.0)

AUC<sub>0-24</sub> = Area under the curve from 0 to 24 hours; C<sub>max</sub> = Maximum plasma concentration; CV% = coefficient of variation in percentages; DRSP = drospirenone; E4 = estetrol; Geo mean = geometric mean; t<sub>1/2</sub> = elimination half life; t<sub>max</sub> = Time of C<sub>max</sub>

**Absorption:** Drospirenone is rapidly and almost completely absorbed. After intake of NEXTSTELLIS, maximum concentrations in serum of about 48.7 ng/mL are reached at about 1-3 h after multiple ingestion. Bioavailability is between 76 and 85%. The rate of absorption in fed conditions is slightly lower than in fasted conditions, and slightly lower peak concentrations are reached. Nonetheless, the overall exposure to drospirenone is similar regardless of food intake around tablet intake of NEXTSTELLIS.

Estetrol is rapidly absorbed after ingestion. After intake of NEXTSTELLIS, average peak plasma concentrations of 17.9ng/mL are reached 0.5-2 hours after single ingestion.

The rate of absorption in fed conditions is slightly lower than in fasted conditions and lower peak concentrations are reached. Nonetheless, the overall exposure to estetrol is similar irrespective of food intake. After this initial absorption phase, lower secondary reabsorption peaks are observed in line with enterohepatic recycling.

**Distribution:** Drospirenone is bound to serum albumin and does not bind to SHBG or corticoid binding globulin (CBG). Only 3-5% of the total serum concentrations of the active substance are present as free steroid. The mean apparent volume of distribution of drospirenone is  $3.7 \pm 1.2$  L/kg.

Estetrol does not bind to Sex Hormone Binding Globulin (SHBG). In a protein binding study by equilibrium dialysis, estetrol displayed moderate binding to human plasma proteins (45.5%-50.4%) and human serum albumin (58.6%), and low binding to human alpha-glycoprotein (11.2%). There is limited distribution of estetrol into red blood cells.

**Metabolism:** Drospirenone is extensively metabolised after oral administration. The major metabolites in plasma are the acid form of drospirenone, generated by opening of the lactone ring, and the 4,5-dihydro-drospirenone-3-sulfate, formed by reduction and subsequent sulfation. Drospirenone is also subject to oxidative metabolism catalyzed by CYP3A4.

After oral administration, estetrol undergoes extensive phase 2 metabolism to form glucuronide and sulphate conjugates. UGT2B7 is the dominant UGT isoform involved in the biotransformation of estetrol into a direct glucuronide. Estetrol undergoes sulfation, mainly by SULT1E1. The two main metabolites, estetrol-3-glucuronide and estetrol-16-glucuronide, have negligible estrogenic activity.

**Elimination:** After oral administration of NEXTSTELLIS, serum drospirenone levels decrease with a terminal elimination half-life observed around 34 hours. The metabolic clearance rate of drospirenone in serum is  $1.5 \pm 0.2$  mL/min/kg. Drospirenone is excreted only in trace amounts in unchanged form. The metabolites of drospirenone are excreted with the faeces and urine at an excretion ratio of about 1.2 to 1.4. The half-life of metabolite excretion with the urine and faeces is about 40 h.

The terminal elimination half-life of estetrol was observed to be around 24 hours under steady state conditions. Following administration of a single oral solution of 15 mg [<sup>14</sup>C]-estetrol, approximately 69% of the total recovered radioactivity was detected as inactive metabolites in urine and 22% in faeces. Therefore, most of the estetrol will be excreted as metabolites with negligible estrogenic activity.

### Special Populations and Conditions

**Pediatrics:** The pharmacokinetics of estetrol and drospirenone in postmenarcheal female adolescents after intake of NEXTSTELLIS have not been investigated.

**Geriatrics:** NEXTSTELLIS is not indicated for this population and hence no specific studies have been conducted.



**Sex:** Not applicable.

**Pregnancy and Breast-feeding:** NEXTSTELLIS is not indicated during pregnancy nor during breastfeeding.

**Genetic Polymorphism:** No data are available.

**Ethnic origin:** No data are available.

**Hepatic Insufficiency:** NEXTSTELLIS is contraindicated in patients with hepatic dysfunction. The mean exposure to drospirenone in women with moderate hepatic impairment is approximately 3 times higher than the exposure in women with normal hepatic function. The mean terminal half-life of drospirenone for women with moderate hepatic impairment was 1.8 times greater than for women with normal hepatic function. No studies were conducted to evaluate the effect of hepatic disease on the pharmacokinetics of estetrol.

**Renal Insufficiency:** NEXTSTELLIS is contraindicated in patients with renal insufficiency. Moderate renal impairment has been shown to increase drospirenone  $C_{max}$  and  $AUC_{0-24}$  by 18% and 37%, respectively. In a single dose study, oral clearance was decreased approximately 50% in volunteers with moderate hepatic impairment as compared to those with normal liver function. No studies were conducted to evaluate the effect of renal disease on the pharmacokinetics of estetrol.

**Obesity:** No data is available. See Warnings and Precautions section regarding Obesity.

## 11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15-30°C). Keep the tablets in their original package. Keep out of reach and sight of children.

### Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Estetrol, once metabolized and eliminated, has no estrogenic effect in the environment.

## 12 SPECIAL HANDLING INSTRUCTIONS

None required.

## PART II: SCIENTIFIC INFORMATION

### 13 PHARMACEUTICAL INFORMATION

#### Drug Substance

#### **Common/Proper name: Estetrol Monohydrate**

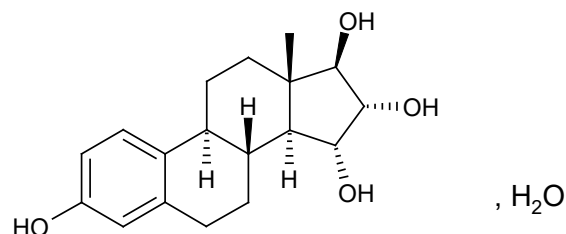
Chemical name:

- IUPAC Name:  
(8R,9S,13S,14S,15R,16R,17R)-13-methyl-6,7,8,9,11,12,14,15,16,17-decahydrocyclopenta[a]phenanthrene-3,15,16,17-tetrol monohydrate
- Other chemical names:
  - Estra-1,3,5(10)-triene-3,15,16,17-tetrol (15 $\alpha$ ,16 $\alpha$ ,17 $\beta$ ) monohydrate
  - Estra-1,3,5(10)-triene-3,15 $\alpha$ ,16 $\alpha$ ,17 $\beta$ -tetrol monohydrate
  - 15 $\alpha$ -hydroxyestriol monohydrate
  - 3,15 $\alpha$ ,16 $\alpha$ ,17 $\beta$ -tetrahydroxyestra-1,3,5(10)-triene monohydrate

Molecular formula and molecular mass: C<sub>18</sub>H<sub>24</sub>O<sub>4</sub>.H<sub>2</sub>O

322.40 g/mol (Estetrol monohydrate)

Structural formula:



Physicochemical properties:

Physical description: Estetrol is a white to off-white crystalline solid.

Solubility: Estetrol is overall poorly soluble in water and aqueous solutions.

Estetrol monohydrate is otherwise soluble in methanol, ethanol, sparingly soluble in acetone and slightly soluble in ethyl acetate and acetonitrile.

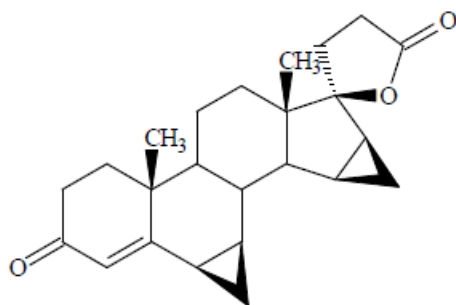
Melting point: 235-247°C

#### **Proper name: Drospirenone**

Chemical name: (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-Hexadecahydro-10,13-dimethylspiro-[17H-dicyclopropa[6,7:15,16]cyclopenta[a] phenanthrene-17,2'(5'H)-furan]-3,5'(2H)-dione.

Molecular formula and molecular mass: C<sub>24</sub>H<sub>30</sub>O<sub>3</sub> and 366.49

Structural formula:



Physicochemical properties:

Physical description: White or almost white crystalline powder.

Solubility: Drospirenone is practically insoluble in water, soluble in methanol, sparingly soluble in ethanol, freely soluble in dichloromethane

Melting point: Drospirenone melting range is between 198° and 203°C.

## 14 CLINICAL TRIALS

### 14.1 Trial Design and Study Demographics

The contraceptive efficacy and safety of NEXTSTELLIS (estetrol monohydrate/drospirenone 15/3 mg) was evaluated in two pivotal phase 3 clinical trials (Study 302 and Study 301). Both trials were similar in study design (see Table 7). The primary efficacy endpoint was the number of on-treatment pregnancies assessed by the Pearl Index (PI) in the ITT Population of women aged 16 to 35 years in Study 302 and 18 to 35 years in Study 301.

**Table 7: Summary of design and subject demographics for pivotal clinical trials**

Study #	Trial design	Dosage, route of administration and duration (28-day cycles)	Study subjects (n)	Mean age (Range) (years)
302	Phase 3, open-label, single-arm, multicenter (77 sites USA and Canada)	Estetrol monohydrate/drospirenone 15/3 mg was supplied as tablets in blister packs with 24 active pink tablets and four white inert tablets.  Oral administration once a daily, 24 active tablets followed by 4 inert tablets (4-day hormone-free interval)  13 consecutive cycles.	1864 (all females)	27.3 (16-50)

Study #	Trial design	Dosage, route of administration and duration (28-day cycles)	Study subjects (n)	Mean age (Range) (years)
301	Phase 3, open-label, single-arm, multicenter (69 sites in Europe and Russia)	Estetrol monohydrate/drospirenone 15/3 mg was supplied as tablets in blister packs with 24 active pink tablets and four white inert tablets.  Oral administration once a daily, 24 active tablets followed by 4 inert tablets (4-day hormone-free interval)  13 consecutive cycles.	1553 (all females)	27.1 years (18-49)

In Study 302, among subjects 16-35 years of age, about 19.5% were African American/black and 26% reported themselves as Hispanic/Latino. About 22.5% of subjects had a BMI  $\geq$  30 kg/m<sup>2</sup>. Approximately 58% of subjects were starters, and approximately 17% of subjects were true new users. The majority of subjects (75.4%) had never smoked, and < 15% were current smokers. In Study 301, among subjects 18-35 years of age, about 0.6% were African American/black and 0.8% subjects reported themselves as Hispanic/Latino. About 5.5% of subjects had a BMI  $\geq$  30 kg/m<sup>2</sup>. Approximately 40% of subjects were starters, and approximately 25% of subjects were true new users. The majority of subjects (77.8%) had never smoked, and < 20% were current smokers.

## 14.2 Study Results

### Pearl Index and Life Table Analysis

The primary efficacy endpoint was the number of on-treatment pregnancies assessed by the Pearl Index in the ITT Population of women aged 16 to 35 years in Study C302 and 18 to 35 years of age in Study C301, inclusive, at the time of screening with at-risk cycles (cycles in which no other methods of birth control and during which the subjects confirmed that sexual intercourse had occurred). The Pearl Index also includes women who did not take the drug correctly. Life table analysis provides a cumulative on-treatment pregnancy rate over one year. Secondary efficacy endpoint included Pearl Index in the overall ITT population.

**Table 8: Summary of primary and secondary analysis of Pearl Index (95% CI) in subjects aged 16 to 35 years with at-risk cycles (ITT Population)**

Primary Analysis of Pearl Index			
	Pooled data (16-35 years of age)	Study 301 (18-35 years of age)	Study 302 (16-35 years of age)
Number of Study subjects with at least one at-risk cycle	2,837	1,313	1,524
On-treatment pregnancy (n)*	31	5	26
Number of at-risk cycles	26,455	13,692	12,763
Pearl Index (primary) and its 95% CI	1.52 (1.04, 2.16)	0.47 (0.15, 1.11)	2.65 (1.73, 3.88)

Life-table analysis: - Cumulative 1-year on-treatment pregnancy rate (%) and its 95% CI - Probability of contraceptive protection after up to 1 year treatment	1.28 (0.83, 1.73)  98.8%	0.45 (0.19, 1.09)  99.6%	2.06 (1.40, 3.04)  97.9%
<b>Secondary Analysis of Pearl Index</b>			
	<b>Pooled data</b> (16-50 years of age)	<b>Study 301</b> (18-50 years of age)	<b>Study 302</b> (16-50 years of age)
Number of Study subjects with at least one at-risk cycle	3,215	1,510	1,705
On-treatment pregnancy (n)*	33	5	28
Number of at-risk cycles	30,286	15,849	14,437
Pearl Index (primary) and its 95%CI	1.42 (0.98, 1.99)	0.41 (0.13, 0.96)	2.52 (1.68, 3.64)

\*Pregnancies with an estimated date of conception within the on-treatment period: Day 1 (initiation of NEXTSTELLIS) to 7 days after the last intake of NEXTSTELLIS (whether active or inactive tablet), inclusive.

### Pearl Index by Subgroup of BMI

No significant association between contraceptive efficacy and BMI was noted. In Study C302 (US/Canada study), Pearl Indices (95% CI) of 2.57 (1.57, 3.97) and 2.94 (1.08, 6.41) were calculated for subjects aged 16 to 35 years with BMI < 30 kg/m<sup>2</sup> and BMI between 30 and 35 kg/m<sup>2</sup>, respectively.

### Bleeding pattern

In pooled 301 and 302 studies, after an initial incidence of 27.1% in Cycle 1, the overall incidence of unscheduled bleeding and/or spotting ranged between 15% and 20% per cycle. The majority of bleeding and/or spotting episodes concerned spotting-only, implying that in each cycle, approximately 90% of the subjects did not experience unscheduled bleeding requiring the use of sanitary protection.

The predictability of vaginal bleeding can be expressed by the occurrence of scheduled bleeding, or by its undesirable complement absence of scheduled bleeding. Absence of scheduled bleeding occurred in 9.7% to 11.3% of subjects per cycle, implying that 88.7% to 90.3% of the women did have their scheduled withdrawal bleeding. There were on average 4.9 to 5.6 scheduled bleeding-spotting days in a cycle, consisting of equal numbers of bleeding and spotting days. The median number of bleeding-spotting days in scheduled episodes was 4.0 to 5.0 days

## **15 MICROBIOLOGY**

Not applicable.

## 16 NON-CLINICAL TOXICOLOGY

### General Toxicology

#### Single-dose studies

Estetrol displayed low acute oral toxicity: a single oral dose of 1000 mg/kg was well tolerated in female rats and in female monkeys.

#### Repeat-dose studies

The long-term toxicity of estetrol, alone and in combination with drospirenone, was investigated after daily oral administration of the following doses.

**Table 9: Overview of Repeat-Dose Toxicity Studies Conducted With Estetrol and Estetrol/Drospirenone**

Species	No./Group	Method of Administration	Treatment Period	Dose (mg/kg/day)
<b>Repeat-Dose Toxicity (Estetrol alone)</b>				
Mouse	12F	Oral (gavage)	2 weeks	3, 10, 30
Mouse	12F	Oral (gavage)	4 weeks	0.03, 0.3, 3, <u>30</u>
Mouse	10F	Oral (gavage)	13 weeks	0.3, 1, 3, 10
Rat	10F	Oral (gavage)	4 weeks	0, 5, <u>15</u> , 50, 150
Rat	10F	Oral (gavage)	13 weeks	0, 0.2, 0.6, 2, 6
Rat	20F	Oral (gavage)	26 weeks	0, 1.5, <u>5</u> , 15
Monkey	4F	Oral (gavage)	4 weeks	0, 5, <u>15</u> , 20
Monkey	6F	Oral (gavage)	13 weeks	0, <u>3</u> , 10, 30
Monkey	8F	Oral (gavage)	39 weeks	0, 1, <u>3</u> , 10
<b>Repeat-Dose Toxicity (Estetrol + Drospirenone)</b>				
Monkey	5F	Oral (gavage)	13 weeks	<i>Estetrol/Drospirenone</i> 0/0, <u>3/0.6</u> , 10/2, 30/6

The highest No Observed Adverse Effect Level (NOAEL) is underlined when determined.

Compound-related findings were generally limited to pharmacologic effects expected following administration of an exogenous estrogen or estrogen/progestogen combination.

Changes observed following administration of estetrol alone included: changes in reproductive tissues weight, generally accompanied by macroscopic and /or microscopic observations (mice, rats, monkeys); minimal to moderate decrease in red blood cell parameters (mice, rats, monkeys) and decrease in white blood cell parameters (rats); decreased thymus weight, associated with lymphoid atrophy (mice, rats, monkeys); increased liver weight (mice, rats) accompanied by microscopic changes and decreased glycogen content (monkeys); changes in adrenals (mice, rats, monkeys). No treatment-related mortality occurred. All the observations were consistent with the estrogenic properties of estetrol and displayed evidence of reversibility upon cessation of treatment, although full recovery to control values was not always reached.

A spectrum of compound-related estrogenic, progestogenic and anti-mineralocorticoid effects was observed following administration of the combination to female monkeys. Hyperglycemia is considered an adverse event and was observed in the repeat dose toxicity study with the

combination, at concentrations significantly higher compared to the human therapeutic dose. In addition, at exposures exceedingly higher compared to the human therapeutic dose, ventricular histological changes, without clinical effects, were observed in monkeys after repeated administration of the combination. Spontaneous ventricular changes are a common observation in the monkey strain used in the study and the observations are possibly related to the genetic background of these monkeys.

Toxicokinetic monitoring showed that, on the basis of AUC<sub>0-24</sub> values, the highest No Observed Adverse Effects Level (NOAEL) determined in rats after 26 weeks of treatment (5 mg/kg/day) and in monkeys after 39 weeks of treatment (3 mg/kg/day) led to 12 times and 5.5 times higher systemic exposure as compared to human exposure at the therapeutic dose. The NOAEL determined in monkeys after 13 weeks of treatment with the combination (3/0.6 mg/kg/day) led to 8 times higher systemic exposure as compared to human exposure to estetrol at the therapeutic dose.

### **Carcinogenicity**

The carcinogenic potential of estetrol was investigated in two-year carcinogenicity studies conducted at oral dose levels of 0, 0.125, 0.25, 0.5 and 1 mg/kg/day in female mice and 0, 0.08, 0.27 and 0.8 mg/kg/day in female rats.

There were no effects on the survival of the animals observed after treatment with estetrol.

Tumorigenic effects of estetrol in mice were manifested by an increased incidence of epithelial and stromal neoplasms in uterine and cervix at  $\geq 0.25$  mg/kg/day and an increased incidence in mammary gland and pituitary gland neoplasms at the high dose (1 mg/kg/day). Treatment of rats with estetrol resulted in an increased incidence of mammary gland adenocarcinomas only at the high dose.

The observed neoplastic and non-neoplastic proliferative findings with estetrol in mammary glands, uterus/cervix and pituitary gland in mice and in mammary glands in rats were consistent with its estrogenic properties.

Carcinogenicity studies were not conducted with the combination estetrol/drospirenone.

### **Genotoxicity**

The mutagenicity of estetrol was investigated *in vitro* in *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, TA102 and in *Escherichia coli* strain WP2 *uvrA* at concentrations up to 5000  $\mu\text{g}/\text{plate}$ . Estetrol showed some indications of a weak and not reproducible genotoxic potential only in *Salmonella typhimurium* strain TA102. The clinical relevance of this *in vitro* observation is unknown.

Estetrol did not induce gene mutations in absence or presence of metabolic activation in a mouse lymphoma assay at concentrations up to 1 mM.

No genotoxic activity of estetrol was demonstrated *in vivo* at high doses (2000 mg/kg). Estetrol was negative in the bone marrow micronucleus test in female rats following single oral administration of 2000 mg/kg. In a Comet assay, estetrol induced no DNA damage or cytotoxicity in rat liver or duodenum.

Drospirenone was negative for genotoxicity in the ICH S2 (R1) standard battery of genotoxicity tests and in the HGPRT test. Drospirenone increased unscheduled DNA synthesis in rat hepatocytes but not in human hepatocytes. The clinical relevance of the observations in rat hepatocytes is considered questionable.

### **Reproductive and development toxicity**

Return-to-fertility upon cessation of treatment with estetrol was demonstrated in rats (1.5 mg/kg/day) and there was no effect on mating, fertility, gestation indices or implantation data.

Estetrol induced maternal toxicity and embryotoxicity (total embryo-fetal loss or abortion) in embryo-fetal development studies in the rat (3 mg/kg/day) and rabbit ( $\geq 0.15$  mg/kg/day). Fetal development delays were noted in both species, but there was no evidence of teratogenic properties.

In a pre-/postnatal development study in rats, parturition difficulties and/or absence of delivery were noted ( $\geq 0.5$  mg/kg/day) leading to mortality or premature sacrifices of F0 females and reduced pup viability on Day 4 post-partum. There were no noteworthy observations in F1 animals with the exception of a slight reduced body weight gain and food consumption in F1 males ( $\geq 0.5$  mg/kg/day).

Drospirenone displays ovulation-inhibitory properties and anti-androgenic activity, and would be expected to reduce fertility in a dedicated study. Effects of estetrol/drospirenone on estrus cycles in female monkeys were reversible.

Drospirenone administered alone or in combination with EE given to pregnant rats during the late stage of gestation caused feminization of male fetuses due to its anti-androgenic properties. As a consequence, DRSP/EE caused a reduced reproductive performance of F1 animals at a dose of 45/0.45 mg/kg/day.



## READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

### PATIENT MEDICATION INFORMATION

#### NEXTSTELLIS

#### Estetrol monohydrate and drospirenone tablets

Read this carefully before you start taking **NEXTSTELLIS** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **NEXTSTELLIS**.

#### Serious Warnings and Precautions

- Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. The risk increases with age, particularly in woman over 35 years of age. The risk also increases with the number of cigarettes smoked. For this reason, women who smoke and are over 35 years of age should not use NEXTSTELLIS.
- Birth control pills DO NOT PROTECT against sexually transmitted infections (STIs), including HIV/AIDS. For protection against STIs, it is advisable to use latex or polyurethane condoms AND take your birth control pills.

#### What is NEXTSTELLIS used for?

NEXTSTELLIS is used to prevent pregnancy in women who:

- Are 16 to 50 years of age, and
- Have had their first menstrual period (menarche).

#### How does NEXTSTELLIS work?

NEXTSTELLIS is a birth control pill. It is considered to be a combination oral contraceptive. This is because it contains two female sex hormones: estetrol monohydrate and drospirenone. The hormone estetrol monohydrate is made from a plant source. NEXTSTELLIS has been shown to be effective in preventing pregnancy when taken as prescribed by your healthcare professional.

Combination hormonal contraceptives, like NEXTSTELLIS work in two ways:

- To stop the monthly release of an egg by the ovaries.
- To change the mucus produced by your cervix. This slows the movement of the sperm through the mucus and through the uterus.

#### Effectiveness of NEXTSTELLIS:

The results of two clinical trials show that about 1 out of 100 women may get pregnant during the first year they use NEXTSTELLIS. The chance of becoming pregnant increases if NEXTSTELLIS is not used correctly.

Women who have a Body Mass Index (BMI) above 35 kg/m<sup>2</sup> were not studied in the clinical trial. It is not known how well NEXTSTELLIS will prevent pregnancy in these women.

#### Other Ways to Prevent Pregnancy:

There are other methods of birth control available. These are usually less effective than birth control pills. If used properly, the other methods of birth control are effective enough for many

women. The following table lists pregnancy rates for different types of birth control. A pregnancy rate is the number of women out of 100 who would become pregnant in one year.

Reported Pregnancies per 100 Women per Year:

Combination pill	less than 1 to 3
Intrauterine device (IUD)	less than 1 to 6
Condom & spermicidal foam or gel	1 to 6
Mini-pill	3 to 6
Condom	2 to 12
Diaphragm with spermicidal foam or gel	3 to 18
Spermicide	3 to 21
Sponge with spermicide	3 to 28
Cervical cap with spermicide	5 to 18
Periodic abstinence (rhythm), all types	2 to 20
No birth control	60 to 85

There are differences in these pregnancy rates. This is because not all people use birth control as carefully or as regularly as they should. This does not apply to IUDs since these are implanted in the uterus. If you are careful and use your birth control regularly, pregnancy rates should be lower. Some types of birth control will require more effort than taking a single pill every day.

**What are the ingredients in NEXTSTELLIS?**

Medicinal ingredients: estetrol monohydrate and drospirenone

Non-medicinal ingredients:

- Pink (active) tablets: Cottonseed oil, hydrogenated, hydroxypropylcellulose, hydroxypropylmethylcellulose, iron oxide red (E172), lactose monohydrate, magnesium stearate, maize starch, povidone, sodium starch glycolate, talc, titanium dioxide (E171)
- White (inert) tablets: Cottonseed oil, hydrogenated, hydroxypropylcellulose, hydroxypropylmethylcellulose, lactose monohydrate, magnesium stearate (E572), maize starch, talc, titanium dioxide (E171)

**NEXTSTELLIS comes in the following dosage forms:**

- Pink tablets: 15 mg estetrol monohydrate and 3 mg drospirenone.
- White tablets: no active ingredient

**Do not use NEXTSTELLIS if:**

- You are allergic to any ingredients in this drug;
- You have or have had a blood clot in the legs (deep vein thrombosis), lung (pulmonary embolism) or somewhere else in your body;
- You have the following risk factors for blood clots:
  - Severe high blood pressure or high blood pressure that is not under control (hypertension);
  - Blood clot disorders such as:
    - Abnormal Factor V Leiden mutation
    - Activated protein C (APC) resistance
    - Antithrombin-III-deficiency
    - Protein C deficiency
    - Protein S deficiency

- hyperhomocysteinemia
- Prothrombin mutation G20210A
- Antiphospholipid-antibodies
- You have an unusual amount of lipoproteins in your blood;
- You have diabetes with complications;
- Increasing age such as a woman older than 50 years old;
- You have too much body fat (you are obese);
- a family history of blood clot disorders;
- You had or will have a major surgery (including to the legs, pelvis or nervous system);
- You cannot stand or move for long periods of time, including prolonged bed rest;
- You are a woman over age 35 and smoke;
- You had a stroke or heart attack;
- You have or had coronary artery disease (including angina) or a condition that may be a first sign of stroke (such as mini stroke, small reversible stroke, chest pains);
- You have a disease of the heart valves with complications;
- You have kidney problems;
- You have adrenal problems;
- You have or you might have breast cancer;
- You have a cancer of the uterus, or a cancer that is sensitive to hormones;
- You have unusual vaginal bleeding without a known reason;
- You have liver disease;
- You have or have a history of liver tumours (cancerous or non-cancerous);
- You have or had jaundice. This is when the skin or whites of the eyes turn yellow. This may have been related to other medicines you were taking or may have happened during pregnancy;
- You have blood vessel disease of the eye that has caused loss of vision;
- You are or think you might be pregnant;
- You have or have had migraine headaches with or without focal aura (flashes of light, blind spots and other vision changes);
- You have or have had inflammation of the pancreas (pancreatitis) and high levels of fat in your blood (triglycerides).

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NEXTSTELLIS. Talk about any health conditions or problems you may have, including if you:**

- have a history of depression
- have a history of kidney problems
- have a history of liver problems
- have a history of adrenal problems
- are obese
- have had or will have a major surgery
- have high blood pressure
- have or have a family history of diabetes
- have migraine headaches
- have hepatitis C and taking drugs for it
- have a family history of blood clot disorders
- have uterine fibroids. These are benign tumours of the uterus
- have inflammatory bowel disease including Crohn's disease or ulcerative colitis

- have sickle cell disease. This is a disease that affects hemoglobin, a molecule in red blood cells that delivers oxygen throughout the body.
- have haemolytic uremic syndrome. This is when there is an abnormal breakdown of blood cells, which clogs the kidney.
- have systemic lupus erythematosus. This is a disease of the immune system.
- have cholestasis. This is a condition where the bile flow from the liver is decreased.
- have a history of seizures or have epilepsy
- have a condition called hereditary angioedema or if you have had episodes of swelling in body parts such as hands, feet, face, eyes or airway passages
- have problems with the valves in your heart and/or have an irregular heart beat
- have porphyria. This is a disease of blood pigment that is passed down in families (inherited)
- have a history of a skin condition called chloasma (hyperpigmentation)
- you are currently on daily, long-term treatment for a chronic condition with any of these drugs:
  - Non steroidal anti-inflammatory drugs (NSAIDs) when taken long-term and for treatment of arthritis or other problems
  - Potassium-sparing diuretics
  - Potassium supplements
  - ACE inhibitors and Angiotensin-II receptor antagonists for the treatment of high blood pressure
  - Heparin

**Other warnings you should know about:**

**Blood clot in legs, lungs, heart, eyes or brain**

Women who use birth control that contains hormones are more likely to develop blood clots. Blood clots are the most common serious side effects of birth control pills. The risk for clots is highest during the first year a woman uses a hormonal birth control. The risk is also high if a woman restarts the same or new hormonal birth control. Clots can occur in many areas of the body and can lead to blindness or impaired vision as well as damage to or loss of a limb and death.

While you are taking NEXTSTELLIS, if you have any of the below symptoms, contact your healthcare professional right away. These are signs of blood clots.

- sharp pain in your chest
- coughing up blood
- sudden shortness of breath
- crushing chest pain or chest heaviness
- irregular heartbeat
- sudden severe or worsening headache
- feeling full
- vomiting
- dizziness, trouble walking
- fainting, seizures
- anxiety, confusion
- changes in vision
- changes in speech

- pain and / or swelling in your calf
- weakness or numbness in your face, arm or leg
- sudden pain, swelling and slight blue or red discoloration of an arm or leg
- discomfort radiating to your back, jaw, throat or stomach

**Cancer:**

Using birth control pills may increase the risk of certain cancers including cancer of the breast, cervix and liver.

**Breast cancer**

The risk of breast cancer in women increases as you get older. It also increases if there is family history of breast cancer, meaning if your mother or sister have or had breast cancer. Other factors that increase your risk for breast cancer are being obese, never having children, or having your first full-term pregnancy at a late age.

If you have breast cancer now, or had it in the past, do not use birth control pills. The hormones in these pills can affect some cancers.

Some women who use birth control pills may have a higher risk of developing breast cancer before menopause. These women may have used birth control pills for a long time (more than eight years), or may have started using birth control pills at an early age.

In a few women, using of birth control pills can speed up the growth of a breast cancer that has not yet been found. Finding breast cancer early can reduce the effect of the cancer on a woman's life expectancy. The risks for breast cancer related to using birth control pills seem to be small. You should, however, have a healthcare professional check your breasts at least once per year.

While you are taking NEXTSTELLIS, check your breasts often. See your healthcare professional if you notice any changes, such as:

- Dimpling or sinking of the skin,
- Changes in the nipple, or
- Any lumps you can see or feel.

**Cervical cancer**

Women who use birth control pills may have a higher chance of getting cervical cancer. However, this may be due to other reasons including infection with the Human Papilloma Virus (HPV). HPV is an important risk factor for cervical cancer. However, it is possible that oral birth control pills may also cause such cancers.

**Liver cancer**

Liver cancer (hepatocellular carcinoma) and liver tumours may be linked to oral birth control pills. The risk for liver cancer increases the longer these pills are used. However liver tumours are extremely rare. If you feel severe abdominal pain or find a lump in your abdomen, contact your healthcare professional right away.

Do not use NEXTSTELLIS if you have a history of liver tumors (cancerous or non-cancerous).

**Gallbladder disease**

The risk for gallbladder disease that needs surgery is higher in women using birth control pills. The risk is highest in the first year of use and increases the longer these pills are used.

**Vaginal bleeding**

Breakthrough bleeding or spotting sometimes happens in women using birth control pills including NEXTSTELLIS. This is blood coming from the vagina between periods. It is most likely to happen in the first months of starting a birth control pill. If the bleeding is heavy or does not stop, contact your healthcare professional.

While you are taking NEXTSTELLIS you may not get your period each month. If you were not taking NEXTSTELLIS as directed by your healthcare professional, you should have a pregnancy test. This will rule out if the missed period is because you are pregnant.

**Pregnancy, Breastfeeding, Miscarriage and Abortions:****Use in pregnancy**

Birth control pills should not be taken by pregnant women. Stop taking NEXSTELLIS if you get pregnant. You should check with your healthcare professional about risks to your unborn child from any medication taken during pregnancy.

**Use after pregnancy, miscarriage or an abortion**

Your healthcare professional will tell you when to start using NEXTSTELLIS after childbirth, miscarriage or an abortion.

**Pregnancy after stopping NEXTSTELLIS**

You will have a menstrual period when you stop using NEXTSTELLIS. Wait until after your next period before getting pregnant. This will help to better date the pregnancy. Speak to your healthcare professional about other forms of birth control you can use during this time.

**Breast feeding**

If you are breastfeeding, talk to your healthcare professional before starting the birth control pill. Other types of birth control, instead of a birth control pill, are recommended until your baby has stopped breastfeeding. The hormones in the pill may lower the amount and quality of your breast milk. This may not happen, however, if you wait until after nursing is established.

**Skin conditions**

Chloasma may develop while you are using NEXTSTELLIS. This appears as yellowish-brown patches on the skin, particularly of the face. It is more likely to happen if you have previously had chloasma gravidarum. This is when these patches appear on the skin of the face during pregnancy. This is commonly known as “the mask of pregnancy”. If you have or had chloasma, avoid too much exposure to the sun while using NEXTSTELLIS.

**Surgery**

Tell your healthcare professional if you are scheduled for surgery. You may need to stop using NEXTSTELLIS one month before surgery and during prolonged bedrest. You may need to wait for at least two weeks after surgery before restarting NEXTSTELLIS.

**Check-ups and tests**

Before starting NEXTSTELLIS, you will need to have examinations and tests. Your healthcare

professional will conduct a physical exam. He or she will examine your breasts, liver, arms and legs. They will conduct a pelvic exam which includes a PAP smear. Your healthcare professional will also ask you some questions about your personal health history and that of your close relatives. He or she will also measure your blood pressure and do blood tests.

While you are taking NEXTSTELLIS, you will need to have regular check-ups with your healthcare professional. Your first check up should be about three months after starting NEXTSTELLIS. Afterward, you will see your healthcare professional about once per year. At these visits, your healthcare professional will conduct physical and internal exams. He or she will also measure your blood pressure and do blood tests.

If you are scheduled for any laboratory tests, be sure to tell your healthcare professional that you are taking NEXTSTELLIS. This is because birth control pills can affect some blood tests NEXTSTELLIS may not work as well as it should to prevent pregnancy if you:

- miss pills,
- don't take your pills as directed by your healthcare professional,
- have gastrointestinal problems, or
- are taking certain medicines.

If this happens, you should use another method of birth control, like condoms (barrier method). Do this while taking NEXTSTELLIS until you start a new pack of NEXTSTELLIS.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with NEXTSTELLIS:**

- drugs used to treat epilepsy including felbamate, lamotrigine, oxcarbazepine, phenytoin, primidone, barbiturates, carbamazepine, topiramate, rufinamide, ethosuximide, phenobarbital;
- drugs used to treat tuberculosis including rifampin, rifabutin;
- drugs used to treat HIV infections including efavirenz, atazanavir/ritonavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, tipranavir/ritonavir, boceprevir, etravirine, nelfinavir, nevirapine;
- alpha-II adrenoreceptor agents including clonidine;
- drugs for Hepatitis C virus including ombitasvir, paritaprevir, ritonavir, with or without dasabuvir, telaprevir;
- drugs used to treat bacterial infections like erythromycin, ampicillin, cotrimoxazole, penicillins, chloramphenicol, neomycin, nitrofurantoin, sulfonamides, tetracyclines, troleandomycin metronidazole;
- drugs used to treat fungal infections like fluconazole, itraconazole, ketoconazole, voriconazole, clarithromycin)
- drugs used to treat fungal infections including griseofulvin;
- drugs used to lower cholesterol levels including clofibrate;
- drugs used to prevent blood clots;
- St. John's Wort, an herbal product used to treat depression and other conditions;
- drugs used to treat diabetes including insulin and oral drugs that lower blood sugar;
- drugs used to help you relax or sleep including benzodiazepines, chlordiazepoxide, lorazepam, oxazepam, diazepam, phenothiazines, reserpine, barbiturates, chloral hydrate, glutethimide, meprobamate;

- drugs used to treat depression including clomipramine;
- drugs used to treat fever, pain or inflammation including acetaminophen, ASA, antipyrene, meperidine, prednisone, phenylbutazone;
- drugs used to treat allergies
- drugs used to treat migraine headaches;
- Folic acid and vitamins E and B<sub>12</sub>;
- drugs used to help prevent organ rejection including cyclosporine;
- a drug used to help treat bleeding called aminocaproic acid;
- drugs used to treat lung diseases such as asthma and COPD (bronchitis, emphysema) including theophylline;
- drugs used to slow the heart rate including isoproterenol;
- drugs used to treat high blood pressure including guanethidine, methyldopa, beta blockers, reserpine, diltiazem and verapamil;
- drugs used to treat high blood pressure in the blood vessels between the heart and the lungs (pulmonary hypertension) including bosentan;
- drugs used to help prevent nausea and vomiting after chemotherapy including aprepitant;
- grapefruit juice

Antacids may affect how NEXTSTELLIS is absorbed in your body. If you need to use antacids, like TUMS, take them 2 hours before or 2 hours after taking NEXTSTELLIS.

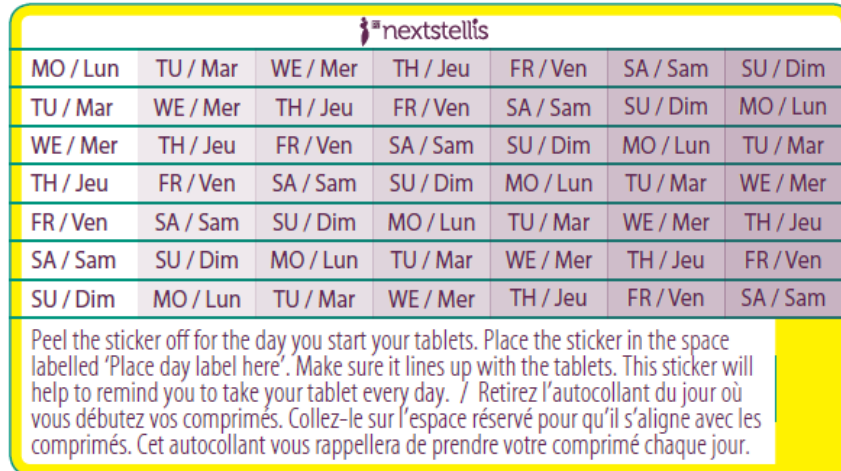
The effects of caffeine and alcohol may also be increased. This is because birth control pills affect how these are metabolized.

### How to take NEXTSTELLIS:

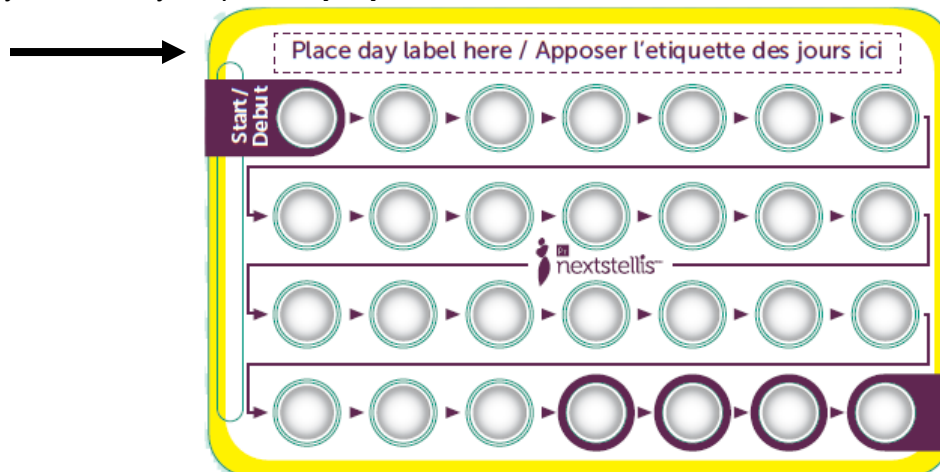
1. **Be sure to read these directions:**
  - before you start taking your pills, and
  - anytime you are not sure what to do.
2. Decide with your healthcare professional what is the best day for you to start taking your first pill. Pick a time of day that will be easy to remember.
3. **Look at your pill pack:**
  - The NEXTSTELLIS pill pack has:
    - 24 pink pills. These pills contain hormones to be taken for 24 days.
    - 4 white pills. These do not contain any hormones and are considered inert. These pills are to be taken for 4 days.
  - Check the pill pack for:
    - where to start taking pills; and
    - the order to take the pills. Follow the arrows.
4. **The first day of your menstrual period (bleeding) is day 1 of your cycle.** Your healthcare professional may tell you to start taking the pills on Day 1 or on the first Sunday after your period begins. If your period starts on Sunday, start that same day.
5. Take one pill at approximately the same time every day for 28 days. Begin a new pack the next day, **NOT MISSING ANY DAYS**. Your period should occur during the last four days of using that pill pack.



6. For Day 1 starters, pick the Day Label sticker that corresponds with the first day of your period. This is the day you start bleeding or spotting. If you are a Sunday starter (your healthcare professional has told you to start NEXTSTELLIS on the Sunday after your period begins), pick the day label sticker that starts with Sunday.



7. Place the Day Label sticker on the top edge of the blister card. This sticker will go over the words: "Place day label here". Labelling the card with the days of the week will help remind you to take your pill everyday.



### 8. Taking NEXTSTELLIS:

- Take NEXTSTELLIS exactly as directed by your healthcare professional.
- Take one pill each day at about the same time.
- Take NEXTSTELLIS with or without food.
- Start taking NEXTSTELLIS on either:
  - Day 1 of your period. This is called "Day 1 start"; or
  - The first Sunday after your period starts. This is called "Sunday start". If your period starts on Sunday, start that same day.
- Take NEXTSTELLIS according to this schedule:
  - i. Take 1 pink tablet each day for 24 days in a row. You should always begin a pack by a pink tablet. You should always take all the pink tablets first.
  - ii. Then, take 1 white tablet each day for 4 days in row.

- iii. Start the next pack on the day after your last white tablet. Take one tablet every day. Do not wait any days between packs. Follow the above schedule with each pack of NEXTSTELLIS.
- Be sure to use all the tablets in each pack.
- Do not skip any days. There is no need to stop taking NEXTSTELLIS for a rest period.
- Do not skip tablets even if you are spotting or bleeding between monthly periods or feel sick to your stomach.
- Do not skip tablets even if you do not have sex very often.

If you start NEXTSTELLIS after Day 1 of your period (Sunday starter):

- Use an extra barrier method of birth control (e.g. condoms) for the first 7 days of your first cycle of NEXTSTELLIS.

You might notice bleeding 2 to 4 days after the last pink tablet. The bleeding might not finish before you start the next pack. This is normal. If this happens, do not stop taking NEXTSTELLIS. These symptoms will usually go away. If they remain for a long time, check with your healthcare professional.

You may miss your period while you are taking NEXTSTELLIS. If you have been having regular periods and then do not have a period for two or more cycles, you may be pregnant. Contact your healthcare professional if this happens.

If you vomit within 4 hours after taking a pink tablet, take **a new tablet as soon as possible**. A new tablet should be taken within 24 hours of the usual dose time. Take the next tablet at the usual dose time. If it has been more than 24 hours since the last tablet was taken, see "**Missed Dose**" below for more instructions.

**Switching to NEXTSTELLIS from a different type of birth control:**

- For any switch, always use a second method of birth control (e.g. condoms) for the first 7 days of taking NEXTSTELLIS.
- If you are switching from another combined oral birth control pill, talk to your healthcare professional about when to start taking NEXTSTELLIS.
- If you are switching from minipill (progestogen only) birth control, start taking NEXTSTELLIS on the next day.
- If you are switching from a type of birth control that is implanted, start taking NEXTSTELLIS on the day the implant is taken out.
- If you switch from a type of birth control that is injected into your body, start taking NEXTSTELLIS on the day the next injection would happen.

**Usual dose:**

Take one (1) tablet per day, starting with the pink tablets. Then, when all the 24 pink tablets are done, take one white tablet per day for 4 days.

**Overdose:**

If too many birth control pills are taken at one time, nausea, vomiting and vaginal bleeding in women are possible.

If you think you, or a person you are caring for, have taken too much NEXTSTELLIS, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

### Missed Dose:

**If you miss pink pills, you could get pregnant.** The more pills you miss, the more likely you are to get pregnant. This is especially true if you miss taking the first few or the last few pink pills in a pack.

Missing pills can cause you to have some spotting or light bleeding, even if you take the missed pills.

The following chart tells you what to do if you miss taking one or more birth control pills. Match the number of pills missed with the appropriate starting time for your type of pill pack. If you miss one or more pink pills and do not have a period that month, you may be pregnant. If this happens, contact your healthcare professional.

Sunday start	Other day than Sunday start
<b>Miss 1 pink pill</b>	
<ol style="list-style-type: none"> <li>1. Take the missed pill as soon as possible and take the next pill at the usual time. This means that you might take two pills on the same day.</li> <li>2. Keep taking one pill a day until the pack is finished.</li> </ol>	
<b>Miss 2 or more pink pills in a row (from Day 1 to Day 17)</b>	
<ol style="list-style-type: none"> <li>1. Take the last missed pill as soon as possible and take the next pill at the usual time. This means that you might take two pills on the same day.</li> <li>2. Keep taking one pill a day until the pack is finished (one or more missed pill(s) will remain in the blister pack).</li> <li>3. <b>Use a back-up barrier method of birth control (such as condom) if you have sex in the 7 days after you miss the pills.</b></li> </ol> <p>You may be pregnant if:</p> <ul style="list-style-type: none"> <li>• You missed pills during Day 1 to Day 7, and</li> <li>• You had unprotected sex during the 7 days before the first missed pill. Tell your healthcare professional right away.</li> </ul>	
<b>Miss 2 or more pink pills in a row (from Day 18 to Day 24)</b>	
<ol style="list-style-type: none"> <li>1. Take the last missed pill as soon as possible and take the next pill at the usual time. This means that you might take two pills on the same day.</li> <li>2. Keep taking one pill per day until the next Sunday.</li> <li>3. On Sunday, discard the pack with missed pills and start a new pack right away.</li> <li>4. <b>Use a back-up barrier method of birth control (such as a condom) until you have taken 7 pink pills in a row.</b></li> </ol>	<ol style="list-style-type: none"> <li>1. Take the last missed pill as soon as possible and take the next pill at the usual time. This means that you might take two pills on the same day.</li> <li>2. Keep taking one pill a day until the active pink pills are used up.</li> <li>3. Discard the four white pills and start a new pack right away.</li> <li>4. <b>Use a back-up barrier contraception method (such as a condom) if you have sex in the 7 days after you miss the pills.</b></li> </ol>

You may not have your period this month. <b>If you miss two periods in a row, you might be pregnant. Call your healthcare professional right away.</b>	You may not have your period this month. <b>If you miss two periods in a row, you might be pregnant. Call your healthcare professional right away.</b>
<b>Miss 1 or more white pills</b>	
Skip the missed pill days and keep taking one pill a day until the pack is finished. No extra birth control method is needed.	

**If you are not sure about the number or the colour of pills missed:**

- Use a barrier method of birth control (such as a condom) until you have taken the pink pills for 7 days.

**Always be sure you have on hand:**

- An extra full pack of pills;
- Back-up methods of birth control. These are types that do not include hormones, like latex or polyurethane condoms and spermicidal foam or gel. You will need back-up birth control if you miss pills and in some other situations. Always talk to your healthcare professional if you are not sure whether you need to use back-up birth control.

**What are possible side effects from using NEXTSTELLIS?**

These are not all the possible side effects you may feel when taking NEXTSTELLIS. If you experience any side effects not listed here, contact your healthcare professional.

- Headache
- Acne
- Skin colour changes, red skin lumps
- Burning, prickling skin feeling
- Excess hair on face, chest, abdomen or legs
- Breast colour change, pain, swelling or tenderness
- Decreased libido
- Weight change
- Nausea and vomiting
- Abdominal or back pain
- Sleep disorder like insomnia or somnolence
- Dizziness
- Hot flush
- Constipation
- Diarrhea
- Black or bloody stools
- Heart burn
- Urinary tract infection
- Flu-like symptoms
- Respiratory tract infections including bronchitis, runny nose, stuffy nose, sore throat
- Dry eyes
- Hair loss
- Bruising
- Bladder spasm
- High or low blood pressure

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>UNCOMMON</b>			
<b>Arterial thromboembolism, Myocardial infarction</b> (blood clot in the artery, heart attack): sudden pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the shoulder, chest, arm, or below the breastbone; discomfort radiating to the back, jaw, throat, arm, stomach, feeling of being full, having indigestion or choking; sweating, nausea, vomiting or dizziness; extreme weakness, anxiety, or shortness of breath; rapid or irregular heartbeats			X
<b>Behavior and mood changes:</b> agitation including aggressive behavior or hostility, changes in sexual desire or sexual activity, increased eating, stress	X		
<b>Breast lumps</b>		X	
<b>Blood clot in the eye:</b> Sudden partial or complete loss of vision			X
<b>Reproductive System Disorders:</b> Pelvic pain, painful intercourse, abdominal bloating or swelling, pain during bowel movements; cysts usually disappear on their own within a few months and may not show symptoms; serious cysts are uncommon		X	
<b>Depression:</b> persistent sad mood accompanied by difficulty in sleeping, weakness, lack of energy, fatigue		X	
<b>Deep vein thrombosis:</b> swelling of one leg or one foot, pain or tenderness in the leg, difficulty standing or walking, feeling of warmth in the leg, red or discolored skin on the leg, sudden pain, swelling and slight			X

blue discoloration of an extremity			
<b>Hypersensitivity</b> (allergic reaction): difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat.		X	
<b>Jaundice:</b> Yellowing of the skin or eyeballs, accompanied frequently by fever, fatigue, loss of appetite, dark-coloured urine, or light-coloured bowel movements		X	
<b>Pulmonary embolism (Blood clot in the lung):</b> Sharp chest pain, coughing of blood, or sudden shortness of breath			X
<b>Stroke:</b> Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness, or numbness in an arm or leg			X
<b>Vaginal bleeding changes:</b> increased or decreased menstrual bleeding, spotting, infrequent periods or absence of bleeding	X		
<b>Vaginal infection</b> (inflammation of the vagina or surrounding area): itching, or unusual or increased vaginal discharge	X		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

### **Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

### **Storage:**

Store NEXTSTELLIS at room temperature (15 - 30°C). Keep the tablets in their original package.

Keep out of reach and sight of children.

Do not throw away any drugs via wastewater or household waste. Ask your pharmacist how to throw away drugs you no longer use. These measures will help to protect the environment.

### **If you want more information about NEXTSTELLIS:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Drug Product Database (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website ([www.searchlightpharma.ca](http://www.searchlightpharma.ca)), or by calling 1-855-331-0830.

This leaflet was prepared by Searchlight Pharma Inc.

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