Rx

NEXTSTELLIS is the **first** and **only** combined oral contraceptive (COC) containing estetrol (E4) in Canada (15 mg E4/3 mg DRSP).[1,2*]

QUESTIONS-ANSWERS ABOUT Pr nextstellis®

Indication

PrNEXTSTELLIS® (estetrol monohydrate [E4] and drospirenone [DRSP]) is indicated for the prevention of pregnancy.[1]

What is the mechanism of action of NEXTSTELLIS?**

NEXTSTELLIS is an E4-containing combined oral contraceptive: 15 mg E4/3 mg DRSP.[1]

- E4 is a naturally occurring estrogen produced in the human fetal liver. It is only produced during human pregnancy and reaches the maternal circulation through the placenta.[1]
- E4 differs from ethinyl estradiol (EE) by the lack of an ethinyl group in the 17-alpha position.[1*]
- E4 in NEXTSTELLIS is an estrogen synthesized from a plant source.[1]

In addition to DRSP, **NEXTSTELLIS contains E4, an estrogen with high selectivity for estrogen receptors**, binding to both ERα and ERβ, with a 4–5 times higher affinity for ERα vs. ERβ. **It acts as an agonist on the vagina, uterus, endometrium, bones, and brain, and an antagonist in breast tissues.[1]**

DRSP is a spironolactone analogue with antimineralocorticoid 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.[1]

What is the demonstrated bleeding/spotting (B/S) pattern with NEXTSTELLIS?

With all COCs, irregular spotting or bleeding may occur, especially during the first months of use. In pooled data from two pivotal studies, after an initial incidence of 27.1% in Cycle 1, the overall incidence of unscheduled B/S ranged between 15% and 20% per cycle.[1†]

- The majority of B/S episodes concerned spotting only. In each cycle, **approximately 90% of the subjects did not experience unscheduled bleeding requiring the use of sanitary protection**.[1]
- 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**.[1]
- 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.[1]

What is the safety profile of NEXTSTELLIS?

The safety of NEXTSTELLIS was assessed by pooling data from two phase 3 and three phase 2 studies (n=3790). Approximately 50% of the subjects reported a TEAE, of which approximately half was judged to be related to NEXTSTELLIS. Less than 10% of TEAEs resulted in premature discontinuation.[1‡]

The most frequently reported adverse reactions (≥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%).[1]

- Patients on NEXTSTELLIS experienced **low rates of trial discontinuation due to acne, weight gain and headache** (0.9%, 0.4%, and 0.4%, respectively).[1]
- 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%).[1]

Related TEAEs experienced by ≥1% of the subjects

Reproductive system and breast disorders	
Metrorrhagia (n=162)	4.3%
Vaginal haemorrhage (n=103)	2.7%
Dysmenorrhoea (n=92)	2.4%
Breast pain (n=79)	2.1%
Breast tenderness (n=67)	1.8%
Menorrhagia (n=51)	1.3%
Gastrointestinal disorders	
Nausea (n=52)	1.4%
Psychiatric disorders	
Libido decreased (n=56)	1.5%
Mood swings (n=50)	1.3%
Nervous system disorders	
Headache (n=123)	3.2%
Skin and subcutaneous tissue disorders	
Acne (n=122)	3.2%
Investigations	
Weight increased (n=75)	2.0%
General disorders and administration site conditions (n=51)	1.3%

TEAE: Treatment Emergent Adverse Event

* Comparative clinical significance has not been established.

** Clinical significance is unknown.

† According to pooled data from two pivotal phase 3, open-label, single-arm, multicenter studies: Study 302 conducted at 77 sites across the United States and Canada and Study 301 conducted across 69 sites in Europe and Russia. In both studies, NEXTSTELLIS was supplied via oral administration, once daily as 24 active tablets followed by 4 inert tablets (4-day hormone-free interval) for 13 consecutive cycles. 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 (n=1864) in Study 302 and 18 to 35 years (n=1553) in Study 301.

‡ Studies conducted in healthy pre-menopausal women (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. 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.

SEARCHLIGHT PHARMA

REVIEWED BY PAAB

What was the efficacy data of NEXTSTELLIS in clinical trials?

NEXTSTELLIS demonstrated a 98.8% probability of contraceptive protection in women after up to one year of treatment (N=2,837[§]; life-table analysis). The Pearl Index (95% CI) in the ITT population (16 -35 years of age) was 1.52 (1.04, 2.16).[1†]

How is NEXTSTELLIS dosed?

NEXTSTELLIS offers the convenience of a 24/4 dosing regimen. One hormone-containing pink tablet is taken each day for 24 consecutive days, followed by one hormone-free white tablet for 4 days. NEXTSTELLIS should be taken at the same time every day, regardless of meal times.[1]

See the Product Monograph for complete dosing and administration information.

Clinical use:

- Safety and efficacy have been studied in women between 16 and 50 years old. No data in women under 16 are available. Use of this product before menarche is not indicated.
- No geriatric data are available. Not authorized for use in women over 50 years of age. NEXTSTELLIS is not indicated for use in postmenopausal women.

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

Most serious warnings and precautions:

Cardiovascular: 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.

Sexually transmitted infections (STIs): Patients should be counselled that birth control pills do not protect against STIs including HIV/AIDS. For protection against STIs, it is advisable to use latex or polyurethane condoms in combination with birth control pills.

Other relevant warnings and precautions:

- **Patients should discontinue NEXTSTELLIS at the earliest manifestation of:**
  - **thromboembolic and cardiovascular disorders**
  - **conditions which predispose to venous stasis and to vascular thrombosis**
  - **visual defects–partial or complete**
  - **papilledema or ophthalmic vascular lesions**
  - **severe headache of unknown etiology or worsening of pre-existing migraine headache**
  - **increase in epileptic seizures**
- 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.
- NEXTSTELLIS should not be used in patients with conditions that predispose to hyperkalemia (e.g., renal insufficiency, hepatic dysfunction, and adrenal insufficiency).
- Consider monitoring serum potassium concentration in high-risk patients who take a strong CYP3A4 inhibitor long-term and concomitantly.
- Women who currently have or have had breast cancer should not use NEXTSTELLIS because breast cancer is a hormonally-sensitive tumour.
- Increased risk for arterial thromboembolism (myocardial infarction) or for cerebrovascular accident (e.g.,transient ischaemic attack, stroke). Arterial thromboembolic events may be fatal.
- The use of any COC carries an increased risk of VTE compared with no use – this risk is highest during the first year a woman ever uses a COC or restarts the same or a different COC.
- For women with multiple risk factors for VTE and ATE: 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.
- Diabetic patients, or those with a family history of diabetes, should be observed closely to detect any worsening of carbohydrate metabolism.
- Alternative contraception should be used in women with severe dyslipoproteinemia.
- Worsening of Crohn's disease and ulcerative colitis has been reported during combined oral contraceptive (COC) use.
- Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology.
- Patients with fibroids (leiomyomata) should be carefully observed.
- Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal.
- Risk of oral contraceptive-related cholestasis. NEXTSTELLIS should be discontinued if jaundice develops.
- Caution is warranted when starting therapy with the Hepatitis C virus (HCV) combination drug regimen ombitasvir, paritaprevir, ritonavir, with or without dasabuvir.
- 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.
- In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms.
- 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. 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 and 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, and at least once a year, or more frequently if indicated thereafter. Follow-up visit examinations 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. Serum potassium concentration should be monitored in high-risk patients who take a strong CYP3A4 inhibitor long-term and concomitantly.
- 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.
- With use of COCs, there have been reports of retinal vascular thrombosis which may lead to partial or complete loss of vision.
- There is an increased risk of thromboembolic complications in COC users after major surgery.
- 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.
- Hormonal contraceptives may cause some degree of fluid retention.
- During the first months of use, irregular spotting or bleeding may occur.
- Chloasma may occasionally occur in women who take COCs, especially in women with a history of chloasma gravidarum.
- If pregnancy occurs while taking NEXTSTELLIS, further intake must be stopped.
- 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.
- The safety and efficacy of NEXTSTELLIS in women with a body mass index (BMI) >35 kg/m^2 has not been evaluated.

For more information:

Please consult the Product Monograph at searchlightpharma.com/app/ uploads/2021/03/ Nextstellis-product-monograph-en-05mar21.pdf for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this piece. The Product Monograph is also available by calling us at 1-855-331-0830.

ITT: intent-to-treat; CI: confidence interval; BMI: body mass index.
§ Number of study subjects with at least one at-risk cycle.

References:
1. NEXTSTELLIS Product Monograph, Searchlight Pharma Inc. December 20, 2024.
2. Searchlight Pharma Inc. Data on File. January 2024.

Nextstellis is a trademark. Searchlight Pharma Inc.,
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EnsembleIQ This Q&A is published by Ensemble IQ, 2300 Yonge Street, Suite 2900, Toronto, ON M4P 1E4, Telephone: 416-256-9908.

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MAT-CA-2301278E