



GET READY FOR THE TAKE-OFF OF ^{Pr}NEXTSTELLIS™: LEARN MORE ABOUT IT

A **new** combined oral contraceptive (COC)
now available in Canada

NEXTSTELLIS (estetrol monohydrate [E4]
and drospirenone [DRSP]) is indicated for
the prevention of pregnancy in women.¹

* Comparative clinical significance has not been established.

The **first** and **only** E4-containing COC in Canada (15 mg E4/3 mg DRSP).^{1,2*}

INTRODUCING NEXTSTELLIS

A novel E4-containing COC: 15 mg E4/3 mg DRSP

- ◆ E4 in NEXTSTELLIS is an estrogen synthesized from a plant source.^{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 ethinylestradiol (EE) by the lack of an ethinyl group in the 17-alpha position.^{1†}

Mechanism of action: In addition to DRSP, NEXTSTELLIS contains E4, which displays a high selectivity for estrogen receptors^{1*}

- ◆ Estrogenic properties of E4 were confirmed in several *in vivo* PD modelling studies.¹
- ◆ E4 displays a **high selectivity** for ERs and binds to both ER α and ER β , with a 4 to 5 times higher affinity for ER α compared to ER β .¹

In vivo PD modelling showed that E4 acts as an **estrogen agonist** on the:¹

- ◆ brain
- ◆ vagina, uterus, endometrium
- ◆ bones



In vivo PD modelling showed that E4 acts as an **estrogen antagonist** in:¹

- ◆ breast tissues



Adapted from the NEXTSTELLIS Product Monograph.¹

* Clinical significance is unknown.

† Comparative clinical significance has not been established.

PD: pharmacodynamic; ER: estrogen receptor.



- ◆ Synthesized from a **plant source**
- ◆ *In vivo* PD modelling showed that it acts as an agonist on the vagina, uterus, endometrium, bones, and brain, and an antagonist in breast tissues*

- ◆ DRSP is a spironolactone analogue with antimineralocorticoid activity
- ◆ No androgenic, estrogenic, glucocorticoid, or antiglucocorticoid activity shown in preclinical animal studies and *in vitro* studies, with the presence of antiandrogenic activity as shown in preclinical studies

**A monophasic
COC comprised
of E4 and DRSP**



NEXTSTELLIS: 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.¹

PHARMACODYNAMIC PROFILE: ENDOCRINE FUNCTION, METABOLIC AND HEMOSTASIS

In single-center, randomized, open-label, three-arm study to evaluate the effect NEXTSTELLIS vs. two reference COCs containing either EE (30 mcg) and LNG (150 mcg) or EE (20 mcg) and DRSP (3 mg) on endocrine function, metabolic control and hemostasis during 6 treatment cycles (N=101 healthy females):^{1*}

Hemostasis parameters¹

- NEXTSTELLIS demonstrated no obvious changes from baseline to Cycle 6 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.

* 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 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/m².

EE: ethinyl estradiol; LNG: levonorgestrel; VWF: von Willebrand factor; TFPI: tissue factor pathway inhibitor; PAI-1: plasminogen activator inhibitor-1; APC: activated protein C; ETP: endogenous thrombin potential; CBG: corticosteroid-binding globulin; SHBG: sex hormone-binding globulin; TBG: thyroxine-binding globulin; HDL: high-density lipoprotein; LDL: low-density lipoprotein; CRP: C-reactive protein; BMI: body mass index.

Endocrine function¹

- No clear changes between baseline and Cycle 6 were observed for endocrine parameters such as dehydroepiandrosterone sulfate, dihydrotestosterone, testosterone, prolactin, free triiodothyronine, free thyroxine and thyrotropin, and cortisol.
- Treatment with 15 mg E4/3 mg DRSP did not result in an apparent decrease in follicle stimulating hormone and luteinizing hormone levels.

Metabolic control¹

Treatment with NEXTSTELLIS resulted in:

- Small increases from baseline to Cycle 6 with respect to liver protein (angiotensinogen and CBG, SHBG, and TBG).
- No apparent change for CRP.
- Little changes from baseline to Cycle 6 in lipid profile parameters (cholesterol, HDL cholesterol, LDL cholesterol, lipoprotein-a, and triglycerides).
- No obvious changes from baseline to Cycle 6 with respect to glucose metabolism parameters such as insulin and glucose level.

DEMONSTRATED EFFICACY OF NEXTSTELLIS – OVERVIEW

Two pivotal phase 3, open-label, single-arm, multicenter studies¹

Summary of design and subject demographics for the pivotal clinical trials

	STUDY 302*	STUDY 301†
Study subjects (n) <i>all females</i>	1,864 (age 16-50)	1,553 (age 18-49)
Dosage	Estetrol monohydrate/drospirenone 15/3 mg	
Route of administration	Oral administration once daily, 24 active pink tablets and 4 white inert tablets	
Duration (28-day cycles)	13 consecutive cycles	
Primary efficacy endpoint	Number of on-treatment pregnancies assessed by the Pearl Index in the ITT Population‡	
	Women aged 16 to 35 years	Women aged 18 to 35 years

* 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 ≥ 30 kg/m². 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.

† 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 ≥ 30 kg/m². 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.

‡ 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.

§ 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.

ITT: intent-to-treat; CI: confidence interval; BMI: body mass index.

Results summary¹

Primary analysis of Pearl Index (95% CI) in subjects (16-35 years of age) with at-risk cycles (ITT Population)

	Primary analysis of Pearl Index		
	Pooled data (16-35 years of age)	Study 302 (16-35 years of age)	Study 301 (18-35 years of age)
Number of study subjects with at least one at-risk cycle	2,837	1,524	1,313
On-treatment pregnancy (n) [§]	31	26	5
Number of at-risk cycles	26,455	12,763	13,692
Pearl Index (primary) and its 95% CI	1.52 (1.04, 2.16)	2.65 (1.73, 3.88)	0.47 (0.15, 1.11)
Cumulative 1-year on-treatment pregnancy rate (%) and its 95% CI	1.28 (0.83, 1.73)	2.06 (1.40, 3.04)	0.45 (0.19, 1.09)
Probability of contraceptive protection after up to 1 year treatment	98.8%	97.9%	99.6%
<p>There was no significant association between contraceptive efficacy and BMI. 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/m² and BMI between 30 and 35 kg/m², respectively.</p>			

NEXTSTELLIS demonstrated a **98.8% probability of contraceptive protection** in women after up to one year of treatment (life-table analysis; ITT population).¹

NEXTSTELLIS SAFETY PROFILE

The safety of NEXTSTELLIS was assessed by pooling data from two phase 3 and three phase 2 studies^{1*}

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.

Related TEAEs experienced by $\geq 1\%$ of the subjects

System Organ Class Preferred Term	PHASE 2 and 3 STUDIES 15 mg E4/3 mg DRSP (N=3,790)	
	n	%
Any Treatment-Emergent Adverse Events	1,056	20.9
Reproductive system and breast disorders	599	15.8
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

* 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.

System Organ Class Preferred Term	PHASE 2 and 3 STUDIES 15 mg E4/3 mg DRSP (N=3,790)	
	n	%
Gastrointestinal disorders	138	3.6
Nausea	52	1.4
Psychiatric disorders	211	5.6
Libido decreased	56	1.5
Mood swings	50	1.3
Nervous system disorders	170	4.5
Headache	123	3.2
Skin and subcutaneous tissue disorders	155	4.1
Acne	122	3.2
Investigations	122	3.2
Weight increased	75	2.0
General disorders and administration site conditions	51	1.3

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

In the pivotal studies for NEXTSTELLIS, medical reasons for discontinuation (n=398, 10.5%) included TEAEs (n=356, 9.4%) and can be divided into TEAEs:¹

- not related to vaginal bleeding (n=250, 6.6%)
- related to vaginal bleeding (n=106, 2.8%)

Other medical reasons included pregnancy (n=41, 1.1%) and death (n=1, 0.03%).

NEXTSTELLIS SAFETY INFORMATION¹

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/m² 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.

SUMMARY

- NEXTSTELLIS contains DRSP and E4, an estrogen that is synthesized from a plant source.¹
- In addition to DRSP, NEXTSTELLIS contains E4, an estrogen with high selectivity for ERs, acting as an agonist on the vagina, uterus, endometrium, bones, and brain, and an antagonist in breast tissues.^{1†}
- In an open-label study, NEXTSTELLIS demonstrated a favourable endocrine function, metabolic and hemostasis pharmacodynamic profile.¹

- In pooled data from two open-label pivotal studies, NEXTSTELLIS demonstrated contraceptive efficacy (Pearl Index 1.52, 95% CI 1.04, 2.16).¹
- In the pivotal studies for NEXTSTELLIS, trial discontinuation related to vaginal bleeding was 2.8%.¹

* Comparative clinical significance has not been established.
† Clinical significance is unknown.
ER: estrogen receptor; CI: confidence interval.



The **first** and **only** E4-containing COC in Canada
(15 mg E4/3 mg DRSP).^{1,2*}

THE JOURNEY
DOESN'T
END HERE.
TO LEARN
MORE, VISIT
NEXTSTELLIS.CA



References: 1. NEXTSTELLIS Product Monograph, Searchlight Pharma Inc. March 5, 2021. 2. Searchlight Pharma Inc. Data on File. April 23, 2021.

SEARCHLIGHT
PHARMA

Searchlight Pharma Inc.
1600 Notre Dame St. West, Suite 312
Montréal, Québec H3J 1M1
www.searchlightpharma.com

Nextstellis is a trademark.
© Searchlight Pharma Inc. 2021
Printed in Canada – September 2021

