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Introducing NEXTSTELLIS®
(drospirenone and estetrol tablets) 3 mg/14.2 mg

PM-US-NEXT-0360 04/24

Disclosures

- This presentation is a promotional program sponsored by Mayne Pharma
- This is not a continuing medical education (CME) program
- I am speaking on behalf of Mayne Pharma and I am being compensated for my time
- Information presented is consistent with US Food and Drug Administration (FDA) guidelines
- Requests for off-label medical information outside the scope of this presentation can be submitted to Mayne Pharma Medical Affairs
- The intended audience is health care professionals

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NEXTSTELLIS®

NEXTSTELLIS is an FDA-approved combined oral contraceptive (COC) containing drospirenone (DRSP) and estetrol (E4)—a novel, selective action, low-impact estrogen

- NEXTSTELLIS is indicated for use by females of reproductive potential to prevent pregnancy
- 24/4 monophasic dosing regimen
- The only contraceptive to contain estetrol (E4)

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning.

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

Additional Important Safety Information will be discussed later in the deck

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Reference: Data on file. Raleigh, NC. Mayne Pharma LLC.

Full Prescribing Information is available at **www.Nextstellis.com**

Introducing Estetrol (E4)

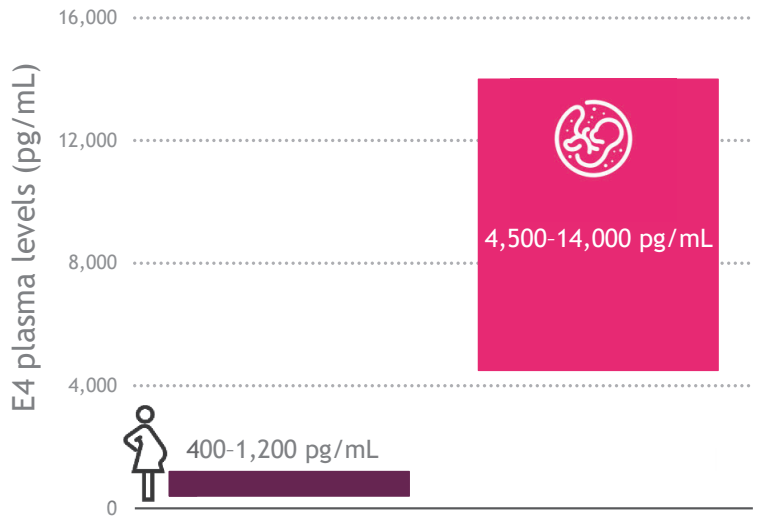
The estrogen that makes NEXTSTELLIS unique

Discovery of Estetrol (E4)—a Native Estrogen

Produced by the fetal liver, estetrol is a native estrogen present from week 9 of gestation[1,4]

- The physiologic function of estetrol has yet to be fully understood[5]

Fetal plasma levels of estetrol are up to **12 times higher** than those of the mother[2,3]



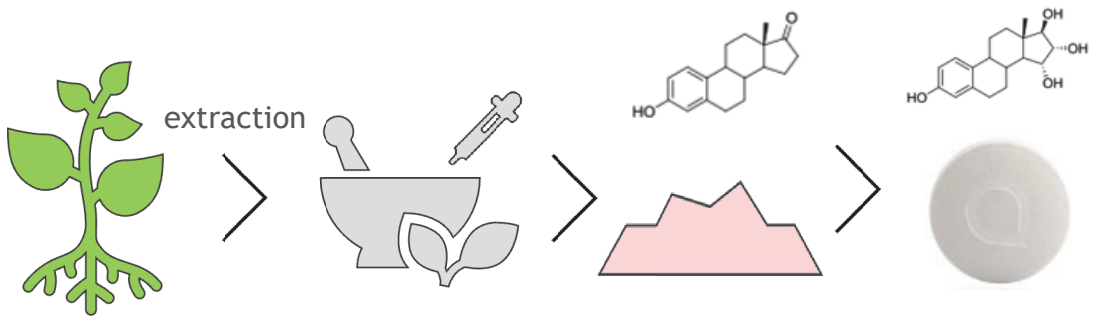
References: 1. Foidart JM, et al. In: *Sex steroids' effects on brain, heart and vessels volume 6: frontiers in gynecological endocrinology*. 2019:169-195. **2**. Tulchinsky D, et al. *J Clin Endocrinol Metab*. 1975;40(4):560-567. **3**. Coelingh Bennink HJ, et al. *Climacteric*. 2008;11(suppl 1):47-58. **4**. NEXTSTELLIS [package insert]. Raleigh, NC: Mayne Pharma; 2021. **5.** Montt-Guevara M, et al. In: Estetrol modulates endothelial nitric oxide synthesis in human endothelial cells, Volume 6 Front. *Endocrinol*. 2015: https://doi.org/10.3389/fendo.2015.00111.

Full Prescribing Information is available at **www.Nextstellis.com**

What Is Estetrol (E4)?

Estetrol is a native human estrogen produced by the fetus during pregnancy[1]

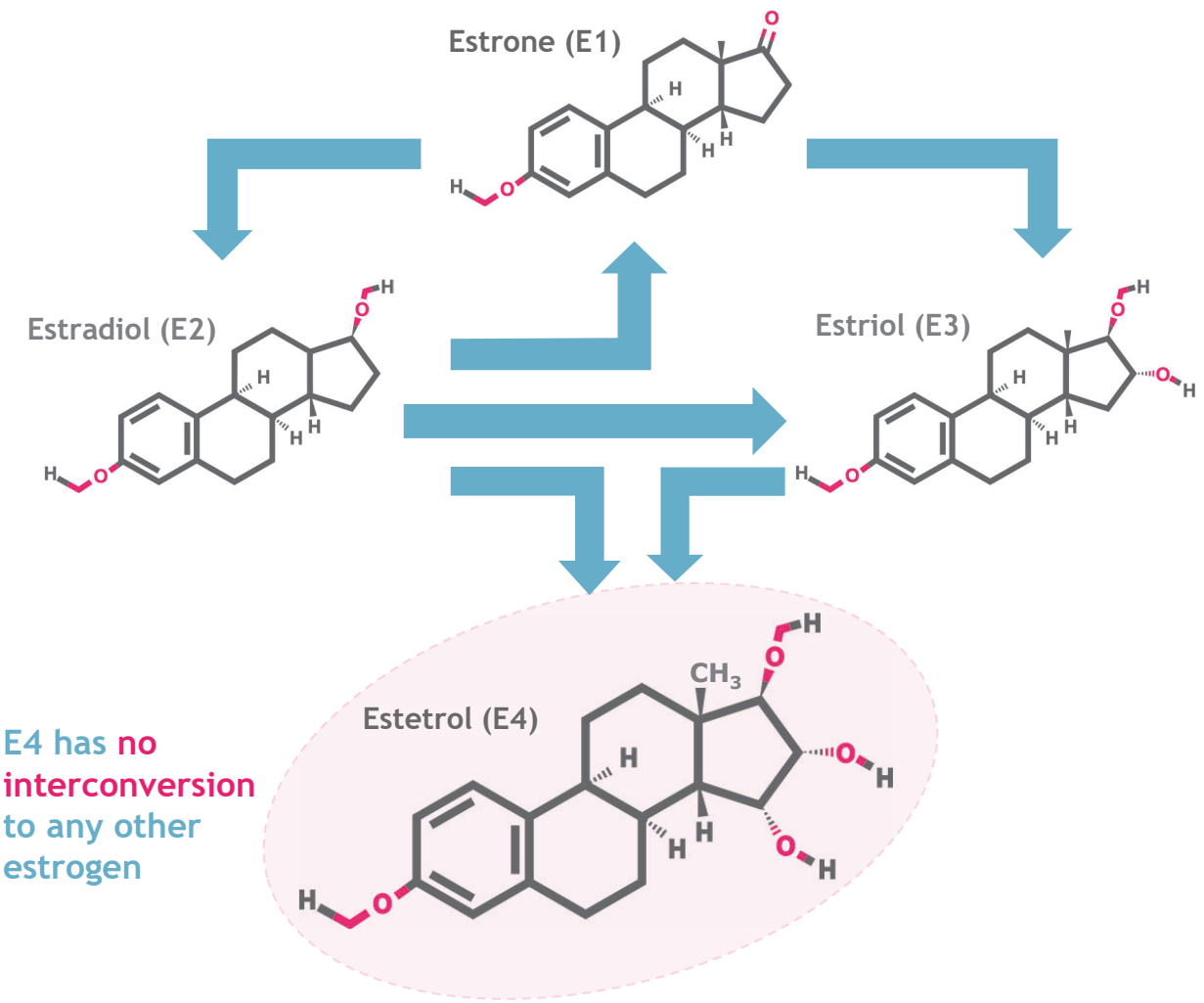
Estetrol in NEXTSTELLIS is a synthetic estrogen manufactured from a plant source[2,3]



References: 1. Coelingh Bennink HJ, et al. *Climacteric*. 2008;11(suppl 1):47-58. **2.** NEXTSTELLIS [package insert]. Raleigh, NC: Mayne Pharma; 2021. **3.** Gerard C, et al. *Expert Rev. Clin. Pharma*col. 2022;15:121-137.

Full Prescribing Information is available at **www.Nextstellis.com**

The Four Native Human Estrogens[1-4]



E4 has no interconversion to any other estrogen

References: 1. Chatuphonprasert W, et al. *Front Pharmacol*. 2018;9:1027. **2.** Coelingh Bennink HJT, et al. *Climacteric*. 2008a;11(suppl 1):47-58. **3.** Thomas MP, et al. *J Steroid Biochem Mol Biol*. 2013;137:27-49. **4.** Stanczyk FZ, et al. *Contraception*. 2013;87(6):706-727

Full Prescribing Information is available at **www.Nextstellis.com**

Estetrol (E4) Has a Unique Pharmacologic Profile

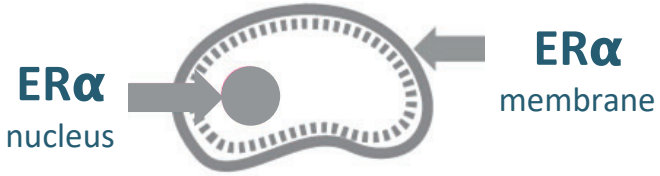
The native characteristics of estetrol (E4) have not required any modification for its use in a contraceptive

Pharmacologic profile[a,b]	Ethinyl estradiol	Estetrol	
Terminal half-life[1,2]	13–27 hours	24–28 hours	Half-life supports daily dose
Hepatic metabolism[3]	Slow, extensive (CYP450 pathway)	Minimal (UGT2B7 pathway)	Minimal hepatic metabolism
Impact on CYP450[3,4]	Extensive	Minimal	Minimal drug interaction
Potency[2,5,b]	500-fold higher than E2	100-fold lower than E2	Lower potency requires mg dosing
Estrogen activity of metabolites[3,4]	Moderate	Negligible	Inactive metabolites

CYP, cytochrome P; E2, estradiol; UGT, UDP-glycosyltransferase. [a]Each contraceptive estrogen has a pharmacologic profile (based on data from nonclinical pharmacology studies in humans and animal models) that informs its use in contraceptive drugs, including dosing and frequency of administration. [b]Potency can vary considerably by tissue type and receptor binding assay.

References: 1. Data on file. Clinical study report MIT-Es0001-C103. Raleigh, NC. Mayne Pharma LLC. **2**. Jusko WJ. *Contraception*. 2017;95(1):5-9. **3.** Stanczyk FZ, et al. *Contraception*. 2013;87(6):706-727. **4.** Coelingh Bennink HJT, et al. *Menopause.* 2017;24(6):677-685 **5**. Abot A, et al. *EMBO Mol Med*. 2014;6(10):1328-1346.

Ethinyl Estradiol (EE) Receptor Activity



Agonist at **all sites**[1]

- Activates both the nuclear and membrane estrogen receptor[1]
- Has estrogenic activity on the vagina, endometrium, bone, vascular system, brain, **liver**, and **breast**[1-3]

ERα, estrogen receptor alpha.

References: 1. Arnal JF, et al. *Physiological Reviews.* 2017;97:3,1045-1087. **2.** Emmanuelle NE, et al. *Int J Mol Sci*. 2021;22(4):1568. **3.** Paterni I, et al. *Steroids*. 2014;90:13-29.

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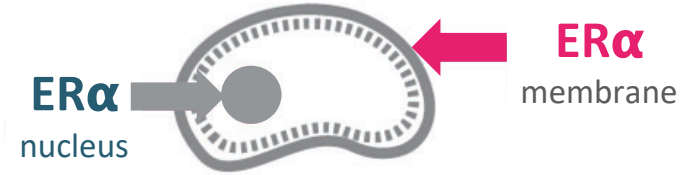
The Unique Dual Role of Estetrol (E4) Results in Tissue Selective Actions



Agonist at the nuclear ERα

- ✓ Activates the nuclear estrogen receptor[1-3]
- ✓ Has estrogenic activity on the **vagina**, **endometrium**, **bone**, **vascular system**, and **brain**[1-3]

Antagonist at the membrane ERα

- ✓ Unlike other estrogens, E4 has a **minimal effect on the liver.** No first pass metabolism—metabolized by UGT pathway[1-3]
- ✓ E4 has a **low impact on breast tissue**[4-7]

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ERα, estrogen receptor alpha; UGT, UDP-glycosyltransferase.

References: 1. Abot A, et al. *EMBO Mol Med*. 2014;6(10):1328-1346. **2.** Foidart JM, et al. In: *Sex steroids' effects on brain, heart and vessels volume 6: frontiers in gynecological endocrinology*. 2019:169-195. **3.** Arnal JF, et al. *Physiol Rev*. 2017;97(3):1045-1087. **4.** Giretti, et al. *Front Endocrinol.* 2014;5:80. **5.** Gérard, et al. *J Endocrinol.* 2015;224:85-95. **6.** Singer CF, et al. *Carcinogenesis.* 2014;35(11):2447-2451. **7**. Visser M, et al. *Horm Mol Biol Clin Invest.* 2012;9(1):95-103.

Full Prescribing Information is available at **www.Nextstellis.com**

Estetrol (E4) Is an Estrogen With Selective Action in Tissues[1-4,a]

Organ	Impact	MOA	Outcome
 Endometrium	HIGH	Estrogen receptor (ER) agonist	Good cycle control[b,c]
 Liver	NEUTRAL	Not metabolized by CYP450 ER mixed antagonist/agonist	**Minimal to no impact on:** Cholesterol[b,c] Triglycerides[b,c] Glucose[b,c] Clotting factors[c] Sex hormone binding globulin[c]
 Breast	LOW	ER antagonist	Inhibits estradiol-induced proliferation[d]

[a]Based on data from nonclinical studies in humans and animal models. [b]Studied paired with a progestin. [c]Women with diabetes mellitus with vascular involvement, diabetes of >20 years duration, or dyslipoproteinemia requiring active treatment with antilipidemic agents were excluded from the study. [d]Based on data from nonclinical studies in animal models.
CYP, cytochrome P; MOA, mechanism of action.

References: 1. Foidart JM, et al. *Frontiers in Gynecological Endocrinology*. New York, NY: Springer International Publishing; 2019:169-195. **2.** Data on file. Clinical study report MIT-Es0001-C302. Mayne Pharma US. Raleigh, NC. **3**. Arnal JF, et al. *Physiol Rev*. 2017;97(3):1045-1087. **4.** Moggs JG, et al. *EMBO Rep.* 2001;2(9):775-781.

Full Prescribing Information is available at **www.Nextstellis.com**

NEXTSTELLIS®
Clinical Development Program

Full Prescribing Information is available at **www.Nextstellis.com**

Estetrol (E4) and NEXTSTELLIS: Extensive Clinical Development Program[1-6]

Phase 1

2005 - 2007

E4 Only

- Single oral dose
- Multiple oral dose
- Proof-of-concept

Four Phase 2 Trials (N=681)

2008 - 2014

E4 + progestins (LNG or DRSP)

2 dose-finding studies evaluating **E4+DRSP** or **LNG**

2 head-to-head studies against **Yaz®** and **Nordette®**

Endpoints included:

- Dose-finding
- Bleeding profile
- Hemostasis, endocrine, and metabolic parameters
- Ovulation inhibition

Two Phase 3 Trials (N=3,632)

2015 - 2020

E4 14.2 mg/DRSP 3 mg

2 pivotal contraceptive trials in US/Canada and EU/Russia

Endpoints included:

- On-treatment pregnancy rate (Pearl Index) in at-risk cycles[a]
- Cycle control (bleeding pattern)[b]
- Safety – AEs[b]
- Subject's well-being[b]

AEs, adverse events; DRSP, drospirenone; LNG, levonorgestrel. [a]Primary endpoint, ages 16-35 years. [b]Secondary endpoints, ages 16-50 years.

References: 1. Apter D, et al. *Contraception*. 2016;94(4):366-373. **2**. Duijkers I, et al. *Eur J Contracept Reprod Health Care.* 2015;20(6):476-489. **3**. Duijkers I, et al. *Contraception.* 2021:S0010-7824(21). **4**. Douxfils, J. et al. *Contraception.* 2020;102(6):396-402. **5.** Klipping C, et al. *Contraception*. 2021;103:213-221. **6.** Data on file. Raleigh, NC. Mayne Pharma LLC.

Full Prescribing Information is available at **www.Nextstellis.com**

Drospirenone (DRSP)

Was selected as the progestin component of NEXTSTELLIS based on results of phase 2 studies comparing estetrol/DRSP with estetrol/LNG[1,2]

LNG, levonorgestrel

References: 1. Douxfils J, et al. *Contraception*. 2020 Dec;102(6):396-402. **2**. Klipping C, et al. *Contraception*. 2021;103(4):213-221.

Full Prescribing Information is available at **www.Nextstellis.com**

Drospirenone (DRSP):
A Progestin Purposely Paired With Estetrol (E4)

Progestin Comparison[1-5]

	Anti-estrogenic	Anti-androgenic	Anti-mineralocorticoid	Half-life (hrs)
Progesterone	+	+	+	16
Drospirenone	+	+	+	~30
Levonorgestrel	+	-	-	32
Norgestimate	+	-	-	12-30
Norethindrone	+	-	-	~9

- **Long half-life of ~30 hours[6]**
- Anti-androgenic[7]
- Anti-mineralocorticoid[8]
- Similar activity to natural progesterone[7]

References: 1. Kuhl H. Pharmacology of estrogens and progestogens: influence of different routes of administration. *Climacteric*. 2005;8(suppl 1):3-63. **2.** Regidor PA, Schindler A. Antiandrogenic and antimineralocorticoid health benefits of COC containing newer progestogens: dienogest and drospirenone. *Oncotarget*. 2017;8(47):83334-83342. **3.** Levy T, Yairi Y, Bar-Hava I, et al. Pharmacokinetics of the progesterone-containing vaginal tablet and its use in assisted reproduction. *Steroids*. 2000;65(10-11):645-649. **4.** Ortho Tri-Cyclen [package insert]. Titusville, NJ: Janssen Pharmaceuticals Inc; October 2013. **5.** Aygestin [package insert]. Pomona, NY: Duramed Pharmaceuticals Inc; July 2007. **6**. Blode H, et al. *Eur J Contracept Reprod Health Care*. 2012;17(4):284-297. **7.** Sitruk-Ware R. *Hum Reprod Update*. 2006;12(2):169-178. **8.** NEXTSTELLIS [package insert]. Raleigh, NC. Mayne Pharma. 2022.

Full Prescribing Information is available at **www.Nextstellis.com**

Select Phase 2 Clinical Trial Results

These results do not represent hard clinical endpoints but are measures of markers, which are only surrogates.

No clinical inferences should be made from the results shown.

Endocrine Effects[1]

6-cycle study (1 cycle = 28 days)
3 arms (E4/DRSP, EE/DRSP, EE/LNG)
n=101 subjects (Age 18-50)
1 cycle washout

Hemostatic Parameters[2]

6-cycle study (1 cycle = 28 days)
3 arms (E4/DRSP, EE/DRSP, EE/LNG)
n=98 subjects (Age 18-50)
1 cycle washout

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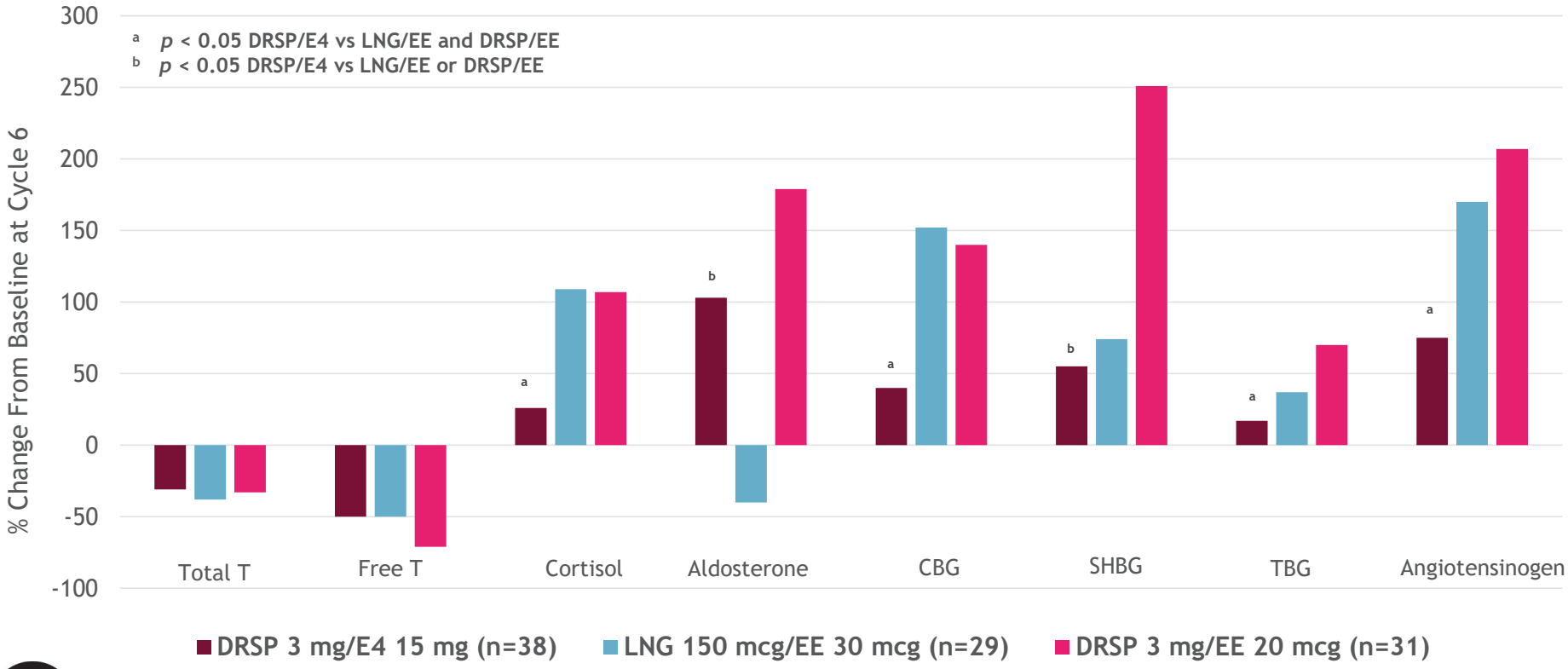
DRSP, drospirenone; E4, estetrol; EE, ethinyl estradiol; LNG, levonorgestrel

References: 1. Klipping C, et al. *Contraception*. 2021;103(4):213-221. **2.** Douxfils J, et al. *Contraception*. 2020 Dec;102(6):396-402.

Full Prescribing Information is available at **www.Nextstellis.com**

Endocrine Effects at Cycle 6 vs Baseline[1,2]

Study Reference: Es0001-C201



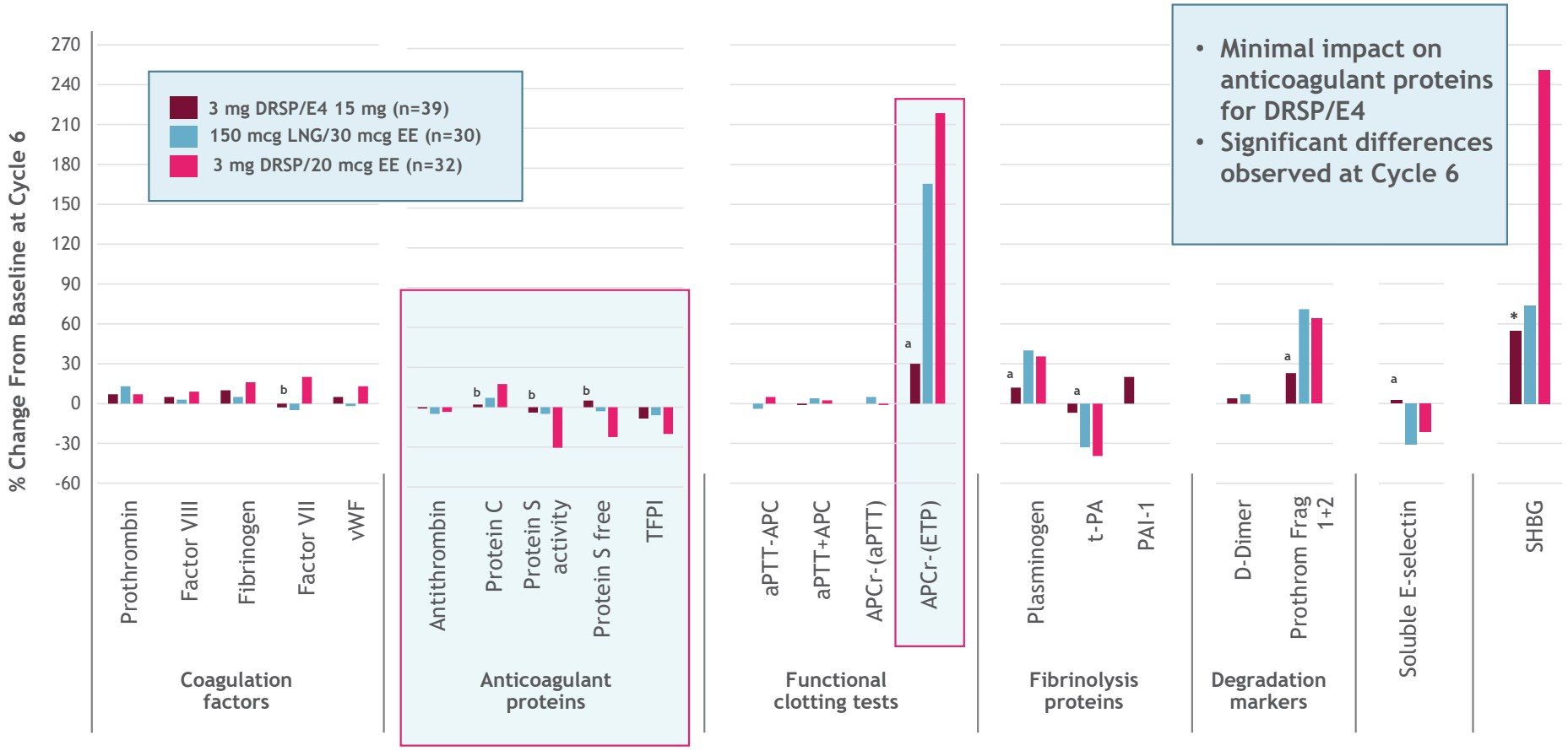
CBG, cortisol binding globulin; DC, discontinuation; DRSP, drospirenone; LNG, levonorgestrel; SHBG, sex hormone binding globulin; T, testosterone; TBG, Thyroid binding globulin.

References: 1. Data on file. Mayne Pharma US. Raleigh, NC. **2**. Klipping C, et al. *Contraception*. 2021;103(4):213-221.

Full Prescribing Information is available at **www.Nextstellis.com**

Impact on Hemostatic Parameters at Cycle 6[1,2]

Study Reference: MIT-Es0001-C201



APCr, activated protein C resistance; aPTT, activated partial thromboplastin time; DRSP, drospirenone; E4, estetrol; EE, ethinyl estradiol; ETP, endogenous thrombin potential; LNG, levonorgestrel; PAI, plasminogen activator inhibitor; SHBG, sex hormone-binding globulin; TFPI, tissue factor pathway inhibitor; t-PA, tissue plasminogen activator; vWF, von Willebrand factor.

[a] $p < 0.05$ DRSP/E4 vs LNG/EE and DRSP/EE

[b] $p < 0.05$ DRSP/E4 vs DRSP/EE

References: 1. Data on file. Mayne Pharma US. Raleigh, NC. **2**. Douxfils J, et al. *Contraception*. 2020 Dec;102(6):396-402

Full Prescribing Information is available at **www.Nextstellis.com**

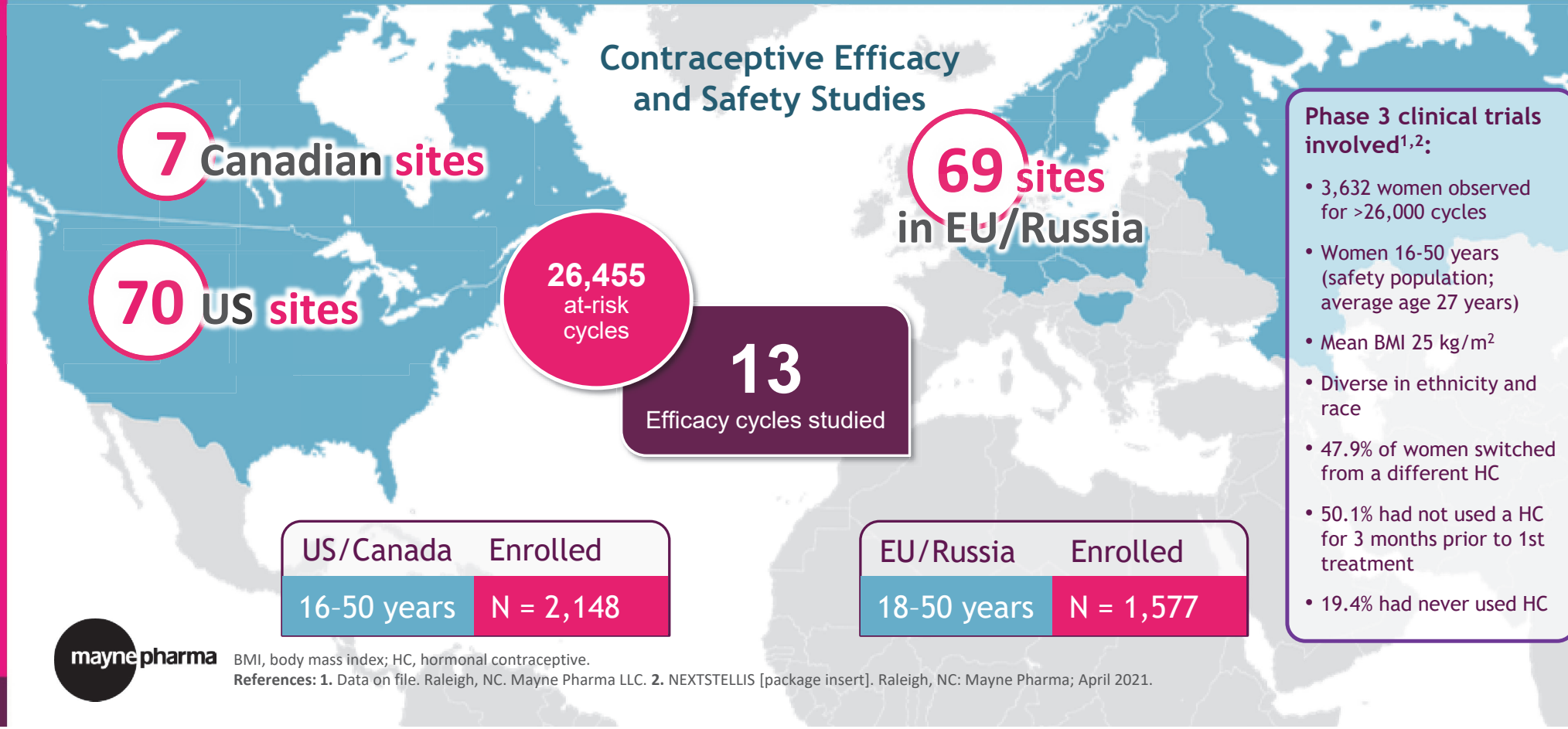
NEXTSTELLIS®

(drospirenone and estetrol tablets) 3 mg/14.2 mg

Efficacy in Phase 3 Clinical Trials

Phase 3 Clinical Studies

Two multicenter, open-label, single arm studies for 13 cycles



US/Canada	Enrolled
16-50 years	N = 2,148

EU/Russia	Enrolled
18-50 years	N = 1,577

Phase 3 clinical trials involved[1,2]:

- 3,632 women observed for >26,000 cycles
- Women 16-50 years (safety population; average age 27 years)
- Mean BMI 25 kg/m^2
- Diverse in ethnicity and race
- 47.9% of women switched from a different HC
- 50.1% had not used a HC for 3 months prior to 1st treatment
- 19.4% had never used HC

BMI, body mass index; HC, hormonal contraceptive.

References: 1. Data on file. Raleigh, NC. Mayne Pharma LLC. **2.** NEXTSTELLIS [package insert]. Raleigh, NC: Mayne Pharma; April 2021.

Phase 3 Study Objectives and Endpoints

Primary objective

Evaluate contraceptive efficacy of NEXTSTELLIS in a 24/4 regimen

Endpoints

Primary (ages 16-35 years) in the North American trial
On-treatment pregnancy rate (Pearl Index) in at-risk cycles

Secondary (ages 16-50 years)
Cycle control–bleeding pattern
Safety–adverse events reporting[a]
Subject's well-being
Broad and inclusive population: age, race, and BMI

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[a]Safety population includes both US/Canada (ages 16-50) and EU/Russia (ages 18-50) phase 3 studies.
Reference: Data on file. Raleigh, NC. Mayne Pharma LLC.

Phase 3: Pearl Index and Contraceptive Efficacy

	US/CA (N = 1,524) 16-35 years
At Risk Cycles	12,763 cycles
PRIMARY ENDPOINT[1]	
Pregnancies, n	26
Pearl Index	2.65
PEARL INDEX BY BMI COHORT[1]	
BMI <30.0 kg/m^2	2.57
BMI 30.0 to 35.0 kg/m^2	2.94

CONTRACEPTIVE EFFICACY

98%[2]

NEXTSTELLIS was effective in preventing pregnancy
(Life Table Calculation)

EFFECTIVE
ACROSS A RANGE OF BODY WEIGHTS[1]

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

BMI, body mass index.

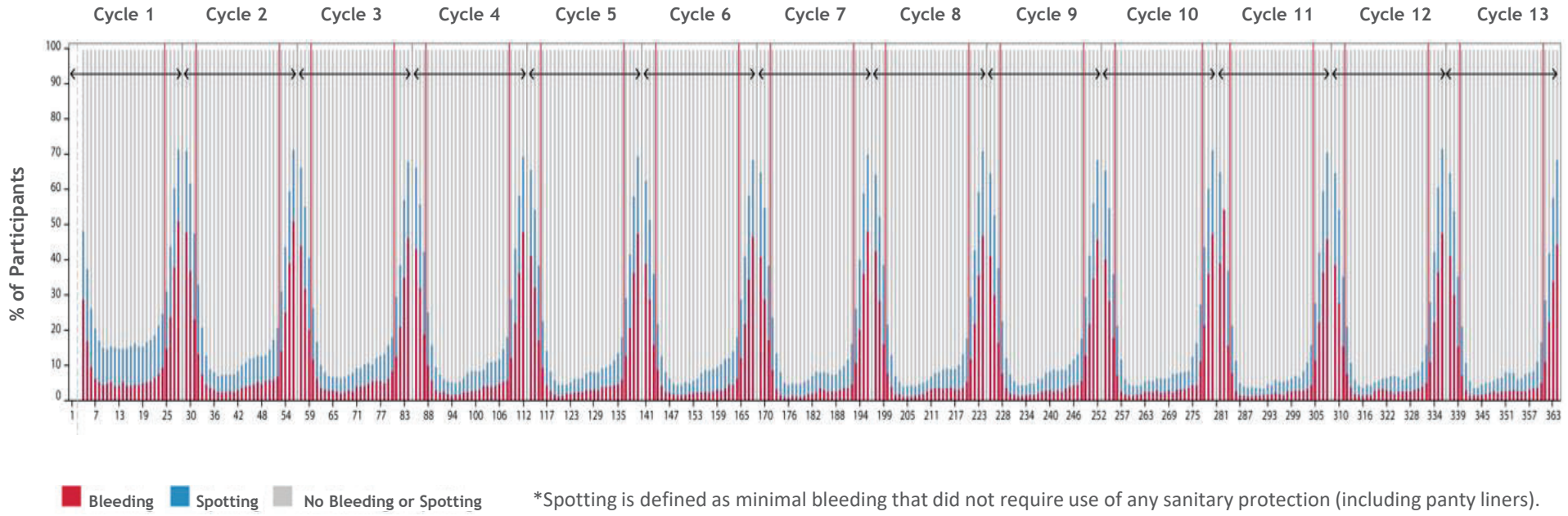
References: 1. NEXTSTELLIS [package insert]. Raleigh, NC: Mayne Pharma; 2022. **2.** Data on file. Raleigh, NC. Mayne Pharma LLC.

Full Prescribing Information is available at **www.Nextstellis.com**

Pooled Analysis of Two Phase 3 Trials (N=3,409)[1,2]

Demonstrates consistency of cycle patterns and the withdrawal bleed

Percentage of participants reporting bleeding or spotting by study day during use of E4/DRSP oral contraception.
Red vertical lines delineate the scheduled bleeding period that occurs between Day 25 and Day 3 of the next cycle.



*Spotting is defined as minimal bleeding that did not require use of any sanitary protection (including panty liners).

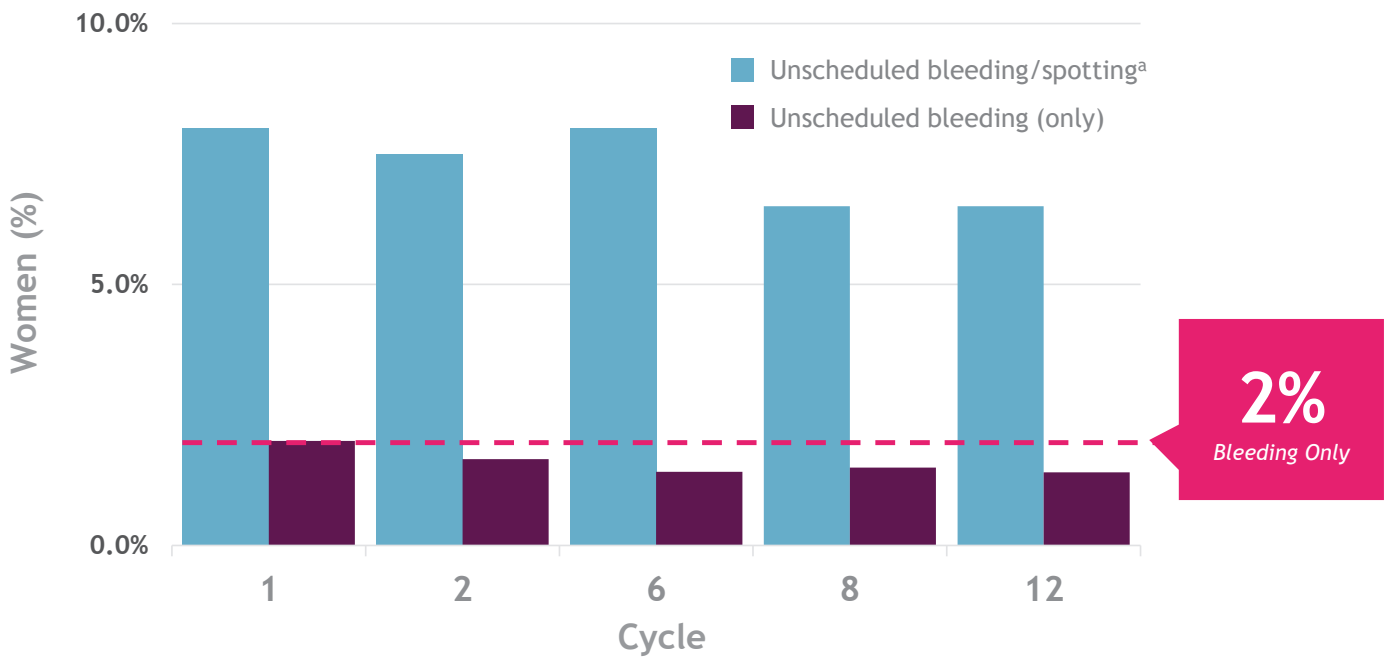
DRSP, drospirenone; E4, estetrol.

References: 1. Kaunitz AM, et al. *Contraception* 2022;116:29-36. **2.** Study Reference: MIT-Es0001-C302.

Full Prescribing Information is available at **www.Nextstellis.com**

US/Canada Phase 3 Study Bleeding Analysis:
Unscheduled Bleeding

% of Participants With Unscheduled Bleeding/Spotting (N=1,864)



TREATMENT DISCONTINUATION

2.8%

of patients withdrew from treatment due to bleeding irregularities

SCHEDULED BLEEDING

85%

of women experienced regular withdrawal bleeding (range: 82% to 87% across cycles)

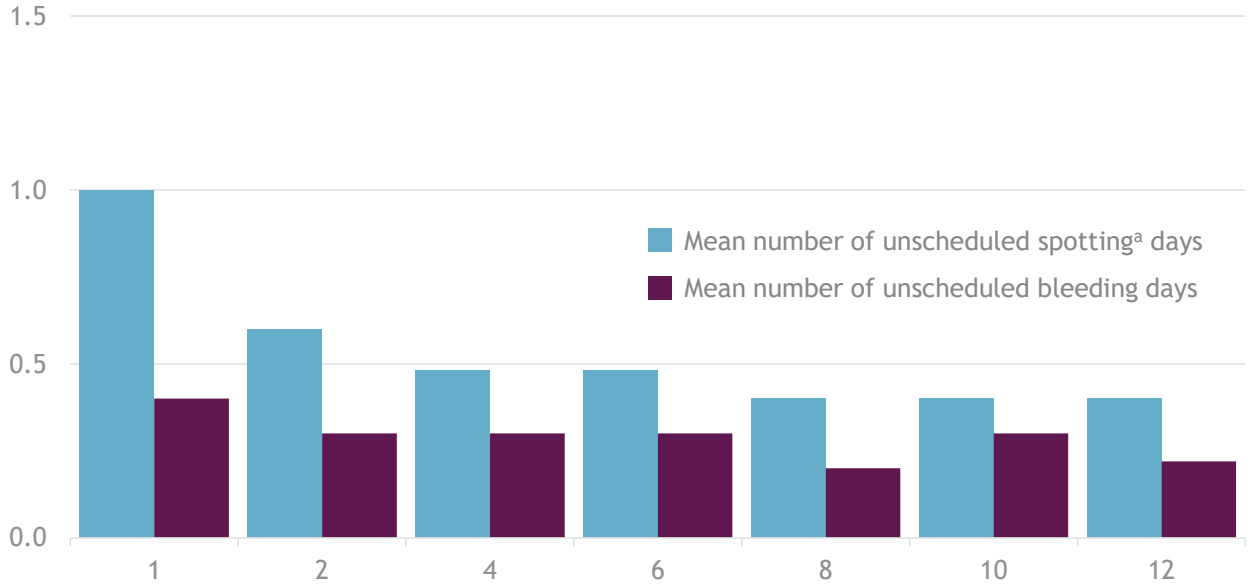
[a]Spotting is defined as minimal bleeding that did not require use of any sanitary protection (including panty liners).

Reference: Data on file. Raleigh, NC. Mayne Pharma LLC.

Full Prescribing Information is available at **www.Nextstellis.com**

US/Canada Phase 3 Study Bleeding Analysis:
Unscheduled Bleeding

Mean Number of Bleeding/Spotting Days per Treatment Cycle (ITT Population) (N=1,756)



AVERAGE DURATION

<1 DAY

of any unscheduled spotting or bleeding on average per cycle after cycle 1.

[a]Spotting is defined as minimal bleeding that did not require use of any sanitary protection (including panty liners).
ITT, intention-to-treat
Reference: Data on file. Raleigh, NC. Mayne Pharma LLC.

Full Prescribing Information is available at **www.Nextstellis.com**

Phase 3 Safety and Tolerability

Adverse Reactions (ARs):
US/Canada and EU/Russia Phase 3 Studies

Preferred Term (PT)[a]	Participants With Adverse Reactions **US/Canada Phase 3 Trial**[b] (n [%]) (N=2,073)	Participants With Adverse Reactions **Two Global Phase 3 Trials**[b] (n [%]) (N=3,632)
Any adverse reaction	1,205 (58.1)	2,126 (58.5)
Mood disturbance	226 (10.9)	329 (9.1)
Bleeding irregularities	201 (9.7)	393 (10.8)
Breast symptoms	110 (5.3)	197 (5.4)
Headache	100 (4.8)	227 (6.3)
Dysmenorrhea	84 (4.1)	133 (3.7)
Weight increased	68 (3.3)	108 (3.0)
Acne	66 (3.2)	136 (3.7)
Libido decreased/lost	27 (1.3)	72 (2.0)

Adverse Reactions (ARs) include all Adverse Events (AEs) reported in ≥2% of participants.
All AEs were included whether drug related or not.

WEIGHT GAIN
<1.1 lb
(N=1,864)

mean weight change through Cycle 6 (visit 5) in the North American Study.

[a]Preferred terms are per MEDRA definitions. [b]Mean duration of NEXTSTELLIS exposure was 257 days (North America) and 317 days (EU/Russia). Average age of study population was 27 years, with a mean BMI of 25 kg/m^2 for both studies. The racial distribution was 83% White; 11% Black; 3% Asian; and 3% Other.

Reference: NEXTSTELLIS [package insert]. Raleigh, NC: Mayne Pharma; 2022.

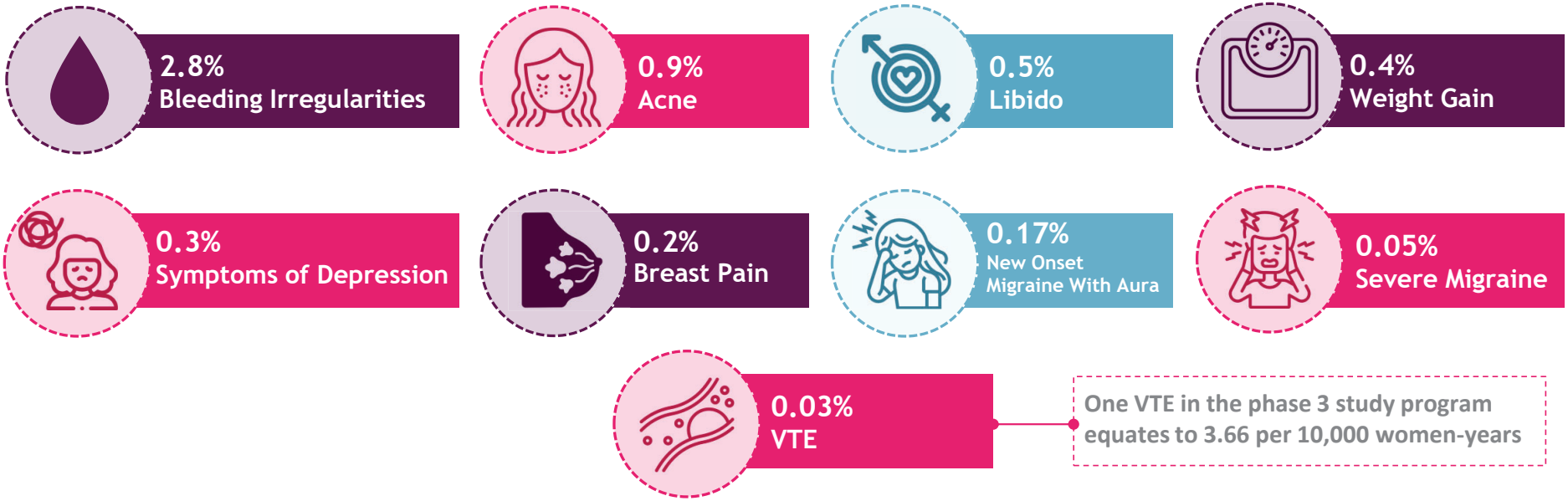
Full Prescribing Information is available at **www.Nextstellis.com**

Very Low Rates of Adverse Reactions Leading to Study Discontinuation

Adverse Reactions Leading to Study Discontinuation

Of 3,632 females (ages 16-50 years) in the two phase 3 studies, only 9.6% discontinued due to an adverse reaction.

The most common reason for discontinuation ≥1% was bleeding irregularity at 2.8%.



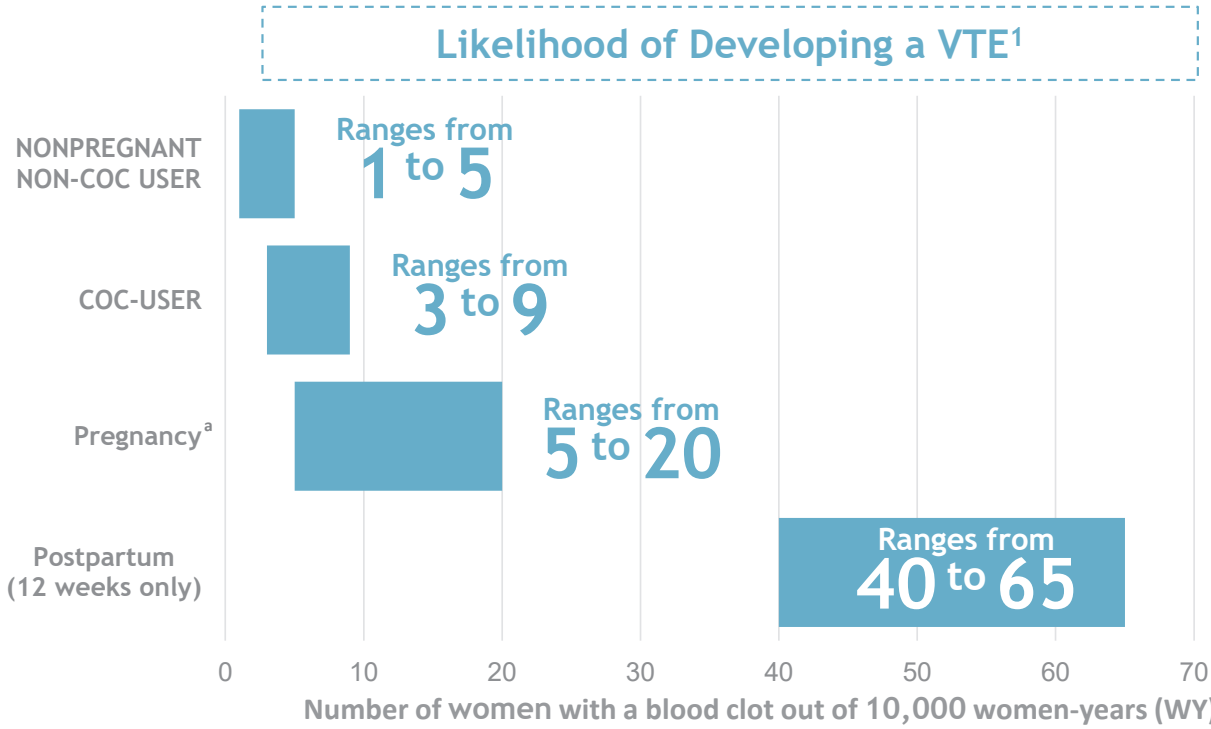
VTE, venous thromboembolism.

Pooled data report average of 302 and 301 CSR data on Related Treatment-Emergent Adverse Events Leading to Discontinuation from the Study Safety Population.

Reference: NEXTSTELLIS [package insert]. Raleigh, NC: Mayne Pharma; 2022.

Full Prescribing Information is available at **www.Nextstellis.com**

Likelihood of VTEs in Women



NEXTSTELLIS VTE RATE[2]

3.66

PER 10,000 WOMEN-YEARS

One VTE in the global phase 3 studies

COC, combined oral contraceptive; VTE, venous thromboembolism.

[a]Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy is 9 months, the rate is 7 to 27 per 10,000 WY.

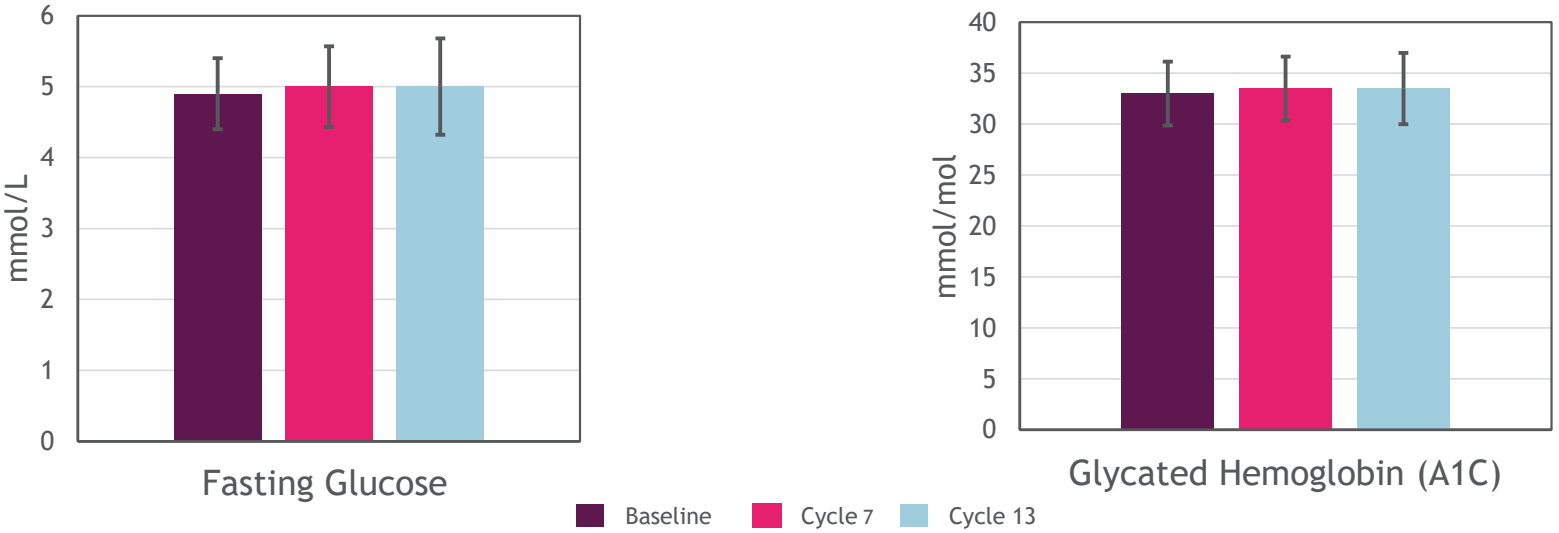
References: 1. NEXTSTELLIS [package insert]. Raleigh, NC. Mayne Pharma LLC. April 2022. **2.** Data on file. Raleigh, NC. Mayne Pharma LLC.

Full Prescribing Information is available at **www.Nextstellis.com**

NEXTSTELLIS®
Additional Clinical Trial Endpoints

US/Canada Phase 3 Study:
Impact on Glucose Metabolism/Tolerance

NEXTSTELLIS had no significant effects on serum fasting glucose or hemoglobin A1C over the 13 cycles of the clinical trial (N=1,864)



Women with diabetes mellitus with vascular involvement or diabetes of >20 years duration were excluded from the study.

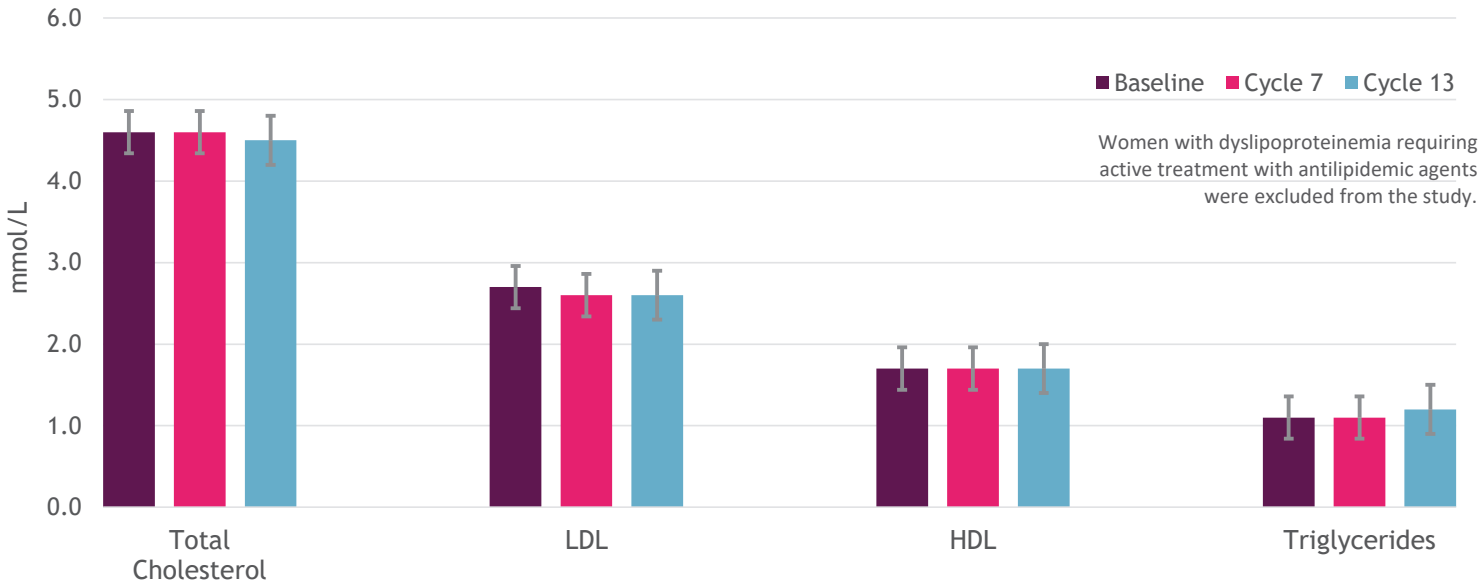
A1C, hemoglobin A1C.

Reference: Data on file. Raleigh, NC. Mayne Pharma LLC.

Full Prescribing Information is available at **www.Nextstellis.com**

US/Canada Phase 3 Study:
Impact on Lipid Metabolism

For women in the phase 3 study, NEXTSTELLIS had minimal impact on lipid metabolism from baseline to Cycle 7 and Cycle 13 (N=1,864)



HDL, High-density lipoprotein; LDL, low-density lipoprotein.

Reference: Data on file. Raleigh, NC. Mayne Pharma LLC.

Full Prescribing Information is available at **www.Nextstellis.com**

Important Safety Information for NEXTSTELLIS®

Full Prescribing Information is available at **www.Nextstellis.com**

Important Safety Information (ISI) for NEXTSTELLIS®

The following ISI is based on the highlights section of the US Prescribing Information for NEXTSTELLIS. Please consult the full Prescribing Information for all labeled safety information for NEXTSTELLIS.

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning.

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

INDICATIONS AND USAGE

NEXTSTELLIS is a combination of drospirenone, a progestin, and estetrol, an estrogen, indicated for use by females of reproductive potential to prevent pregnancy.

Limitations of Use

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

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Full Prescribing Information is available at **www.Nextstellis.com**

Important Safety Information (Cont.)

CONTRAINDICATIONS

- A high risk of arterial or venous thrombotic diseases
- Current or history of a hormonally sensitive malignancy (eg, breast cancer)
- Hepatic adenoma, hepatocellular carcinoma, acute hepatitis, or decompensated cirrhosis
- Coadministration with hepatitis C drug combination (ombitasvir/paritaprevir/ritonavir, with or without dasabuvir)
- Abnormal uterine bleeding that has an undiagnosed etiology
- Renal impairment
- Adrenal insufficiency

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Important Safety Information (Cont.)

WARNINGS AND PRECAUTIONS

Thromboembolic Disorders and Other Vascular Problems: Stop NEXTSTELLIS if a thrombotic or thromboembolic event occurs. Start no earlier than 4 weeks after delivery. Consider all cardiovascular risk factors before initiating in any female, particularly in the presence of multiple risk factors.

Hyperkalemia: Check serum potassium concentration during the first NEXTSTELLIS treatment cycle in females on long-term treatment with medications that may increase serum potassium concentration.

Hypertension: Monitor blood pressure periodically and stop use if blood pressure rises significantly.

Migraine: Discontinue if new, recurrent, persistent, or severe migraines occur.

Hormonally Sensitive Malignancy: Discontinue NEXTSTELLIS if a hormonally sensitive malignancy is diagnosed.

Liver Disease: Withhold or permanently discontinue for persistent or significant elevation of liver enzymes.

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Important Safety Information (Cont.)

WARNINGS AND PRECAUTIONS (CONT.)

Glucose Tolerance and Hypertriglyceridemia: Monitor glucose in females with prediabetes or diabetes. Consider an alternate contraceptive method for females with hypertriglyceridemia.

Gallbladder Disease and Cholestasis: Consider discontinuing NEXTSTELLIS in females with symptomatic gallbladder or cholestatic disease.

Bleeding Irregularities and Amenorrhea: May cause irregular bleeding or amenorrhea. Evaluate for other causes if symptoms persist.

ADVERSE REACTIONS

Most common adverse reactions (≥2%): Bleeding irregularities, mood disturbance, headache, breast symptoms, dysmenorrhea, acne, weight increased, and libido decreased.

Full Prescribing Information is available at **www.Nextstellis.com**

Important Safety Information (Cont.)

DRUG INTERACTIONS

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

This is not a comprehensive list of safety information related to NEXTSTELLIS.

Please See Full Prescribing Information, including BOXED WARNING.

To report **SUSPECTED ADVERSE REACTIONS**, call 1-844-825-8500 or report via the FDA MedWatch Program at www.fda.gov/medwatch or 1-800-FDA-1088.

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Summary

NEXTSTELLIS®
The first and only COC to contain estetrol (E4)

Estetrol, a selective action, low-impact, native estrogen[1]

Native

Estetrol is a native estrogen that:

Circulates at high levels in mother and fetus during pregnancy

Is a synthetic estrogen manufactured from a plant source[2,3]

NEXTSTELLIS is the first COC to contain estetrol (E4)

Selective

Estetrol is a low-impact estrogen that supports:

Bone
Brain
Uterus/vagina
Vascular system

+

Does not stimulate breast tissue[a]

+

Free from clinically relevant CYP450 activity

[a]Based on data from nonclinical studies in humans and animal models.
COC, combined oral contraceptive; CYP, cytochrome P.

References: 1. Data on file. Raleigh, NC. Mayne Pharma LLC. **2.** NEXTSTELLIS [package insert]. Raleigh, NC: Mayne Pharma; 2021.
3. Gerard C, et al. *Expert Rev. Clin. Pharma*col. 2022;15:121-137.

Full Prescribing Information is available at **www.Nextstellis.com**

NEXTSTELLIS®:
What's Next in Birth Control

NEXTSTELLIS is the ideal pairing of estetrol and drospirenone, delivering an **effective** and **safe** combined oral contraceptive with a unique pharmacologic profile

Proven Efficacy

- **98%** effective in preventing pregnancy with a 24/4 monophasic regimen
- **85%** of women experienced a regular, scheduled withdrawal bleeding
- **90%** of women experience no breakthrough bleeding/spotting[a]
- **<1 Day** of any unscheduled spotting or bleeding on average per cycle after Cycle 1

Proven Safety

- Well-tolerated with **low rates of adverse reactions**, including acne (3.7%), weight gain (3.0%), and decreased libido (2.0%)
- Women experienced **minimal changes** in cholesterol, triglycerides, glucose, and glycated hemoglobin
- **Low discontinuation rates** due to adverse reactions: total discontinuation (9.6%), any bleeding irregularity (2.8%), breast pain (0.2%), and VTE (0.03%)

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[a]Spotting is any light bleeding that does not require the use of sanitary protection, including panty liners.
VTE, venous thromboembolism.
Reference: Data on file. Raleigh, NC. Mayne Pharma LLC.

Full Prescribing Information is available at **www.Nextstellis.com**

Accessing NEXTSTELLIS®

NEXTSTELLIS® Savings Programs

With the NEXTSTELLIS Savings Program, covered, eligible patients may pay as little as $0 for each 1-month or 3-month prescription fill

TEXT "NEXT" TO 60323†

$0 Copay* for most eligible **covered** patients

$25* for most eligible **uncovered** patients

RxBIN: **637765**
RxPCN: **CRX**
GRP: **TCWMRE1**
ID: **REWB2222**

nextstellis®
(drospirenone and estetrol tablets)
3 mg/14.2 mg

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*Restrictions and limitations apply. Please see reverse side for Terms, Conditions, and Eligibility Criteria.

†One message per request. Recurring messages after sign up is complete. Message and data rates apply.

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Reference: Data on file. Raleigh, NC. Mayne Pharma LLC.

Request preactivated Savings Cards from your Mayne Pharma representative

or

www

Patients can sign up for the Savings Card online at https://www.nextstellis.com/savings

or

Healthcare Providers: Send your patients' prescriptions to GoodRx Prescription Services or Blink Rx. For local pharmacies in our network, simply contact your Mayne Pharma Representative.

GoodRx

E-Prescribe to GoodRx Prescription Services:
GoodRx
2400 Sand Lake Road, Suite 200
Orlando, FL 32809
NCPDP #5755523

Call the Prescription in to:
1 (877) 219-7537

Fax the Prescription Request Form to:
1 (877) 219-7548

BLINKRX

E-Prescribe to Blink:
BlinkRx
4696 Overland Road, Suite 274
Boise, ID 83705
NCPDP #6008925

Call the Prescription in to:
1 (844) 667-9575

Fax the Prescription Request Form to:
1 (866) 585-4631

Full Prescribing Information is available at **www.Nextstellis.com**

Supporting Equitable Access to Contraceptives

- In January 2023, the US Departments of Labor, Health and Human Services, and Treasury began enforcement of the 2022 guidance to remove barriers to preventative care and contraception for women
- New guidance reinforces the requirement that plans must cover any contraceptive services and FDA-approved, cleared, or granted contraceptive products that a patient and their provider have determined to be medically appropriate without cost-sharing
- Plans **may not** use "Unreasonable Medical Management Techniques" in their determination, which include:
  - Denying coverage for newer or brand name contraceptives
  - Applying age-related restrictions for a contraceptive service or product
  - Requiring patients to satisfy a step-therapy or "fail first" approach

Reporting of Violations:

Consumers covered by a private sector, employer-sponsored group health plan	Contact the Department of Labor (DOL) at www.dol.gov/agencies/ebsa/about-ebsa/ask-a-question/ask-ebsa or call toll free at 1-866-444-327
Consumers covered by fully-insured coverage	Go to https://content.naic.org/state-insurance-departments to find contact information for the appropriate State Department of Insurance

Reference: https://www.cms.gov/files/document/faqs-part-64.pdf; Accessed on April 17, 2024.

Q & A