NEW DRUG APPROVAL

Brand Name	Nextstellis®
Generic Name	drospirenone and estetrol
Drug Manufacturer	Mayne Pharma LLC and Mithra Pharmaceuticals

New Drug Approval

FDA Approval Date: April 15, 2021

Review Designation: Standard

Review Type: Type 1 - New Molecular Entity; New Drug Application (NDA): 214154

Dispensing Restriction: Open Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

In 2017–2019, approximately 65% of women aged 15–49 years were currently using contraception. The options for contraception have increased dramatically over the past several decades. Choices of reversible birth control include intrauterine devices (IUDs), hormonal methods (implants, intrauterine contraceptives, injections, oral contraceptives, transdermal patches, and intravaginal rings), and barrier methods (diaphragms, condoms, caps, sponges, and spermicides). In addition, natural birth control methods include fertility awareness, the withdrawal method, and the lactation amenorrhea method. The most common reversible birth control methods used among women aged 15–49 years were the oral contraceptive pill; long-acting reversible contraceptives, which include implants and intrauterine devices; and male condoms.

Efficacy

The efficacy and safety of Nextstellis® were evaluated in 2 multicenter, open-label, single-arm Phase 3 trials: E4 freedom in the United States/Canada (C302; NCT02817841) and in the European Union (EU)/Russia (C301; NCT02817828).

Table. Nextstellis® E4 FREEDOM Clinical Study in the United States/Canada

Study Population	**Study C302 (NCT02817841):** Prospective, multicenter, open-label, single-arm, 1-year study in North America that enrolled 1674 female participants 16 to 35 years of age. ○ Mean age, 25.8 years ○ Mean BMI, 25.8 kg/m^2 ○ 70.1% Caucasian ○ 19.5% Black or African American ○ 4.8% Asian ○ 0.9% American Indian or Alaska native ○ 0.4% Native Hawaiian or other Pacific Islander ○ 4.2% other

Interventions	15 mg E4 and 3 mg DRSP tablets administered once daily for 13 consecutive cycles following a 24/4-day regimen, i.e. one 15 mg E4/3 mg DRSP active tablet per day for 24 consecutive days followed by one placebo tablet per day for 4 consecutive days.
Endpoints	**Primary:** Pearl Index* = number of pregnancies per 100 women-years of treatment

*The lower the Pearl Index, the higher the effectiveness of the birth control method.
Abbreviations: BMI, body mass index; DRSP, drospirenone; E4, estetrol.

In Study C302, a total of 26 on-treatment pregnancies occurred in 1524 females. The overall Pearl Index was 2.65 (95% confidence interval [CI]: 1.73–3.88) per 100 woman-years of use. A trend of decreasing effectiveness with increasing BMI was observed in the study. The efficacy results for Study C302 are summarized in Table.

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

Subgroup	Number of Patients	On-Treatment Pregnancies	At-Risk Cycles	Pearl Index (95% CI)
Entire study population	1524	26	12,763	2.65 (1.73, 3.88)
BMI (kg/m²)				
<30	1187	20	10,113	2.57 (1.57, 3.97)
≥30 to <35*	337	6	2650	2.94 (1.08, 6.41)

*One female with a BMI of 48 kg/m2 was enrolled and included in the efficacy analysis.

Safety

ADVERSE EVENTS

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

WARNINGS & 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 enzyme.
- 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.

CONTRAINDICATIONS

Nextstellis® is contraindicated in females who develop or are known to have:

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

Clinical Pharmacology

MECHANISMS OF ACTION

Combined hormonal contraceptives (CHCs) prevent pregnancy primarily by suppressing ovulation.

Dose & Administration

ADULTS

- Day 1 start, take 1 active (drospirenone 3 mg/estetrol 14.2 mg) pink tablet by mouth at the same time daily for 24 days, followed by 1 inactive white tablet daily for 4 days, then repeat the 28-day cycle starting on the same day of the week as the first cycle pack.
- No current use of hormonal contraception: Take the first active pink tablet on the first day of menses. Utilize a back-up nonhormonal contraceptive (NHC) for the first 7 days of treatment if started anytime other than on the first day of menses.
- Switching from other hormonal contraceptives: Initiate treatment on the day when a new pack of combined oral contraceptives would have started or after the last progestin-only oral tablet was taken, on the day when the next transdermal system, vaginal insert, or injection would have been scheduled, or on the day of removal of an intrauterine system or implant.
- Initiation following delivery, abortion or miscarriage: Begin no earlier than 4 weeks after delivery (greater than 20 weeks gestation) in women who are not breastfeeding or after a second trimester abortion or miscarriage (greater than 14 weeks to 20 weeks gestation) and use NHC for the first 7 days of treatment if menstrual cycles have not yet resumed. Use NHC for 7 days if treatment is initiated within 7 days following a first trimester abortion or miscarriage (14 weeks or less gestation).

PEDIATRICS

Safety and efficacy of Nextstellis® have been established in females of reproductive potential only (16-50 years). If after menarche, refer to adult dosing.

GERIATRICS

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

RENAL IMPAIRMENT

Nextstellis® is contraindicated in females with renal impairment.

HEPATIC IMPAIRMENT

Nextstellis® is contraindicated in females with hepatic impairment.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

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

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