PDL DRUG REVIEW

Proprietary Name: Nextstellis®
Common Name: drospirenone and estetrol
PDL Category: Contraceptives- Monophasic Combination O/Cs

Comparable Products	Preferred Drug List Status
Drosperinone-EE Tab 3-0.02mg	Preferred
Drosperinone-EE Tab 3-0.03mg	Preferred

Summary

Pharmacology/Usage: Nextstellis® is an oral contraceptive that contains drospirenone (a spironolactone analogue with anti-mineralocorticoid and antiandrogenic activity) and estetrol (a synthetic analogue of a native estrogen present during pregnancy that is selective for nuclear estrogen receptor-α (ER-α) and ER-β). Combined hormonal contraceptives (CHCs) prevent pregnancy primarily by suppressing ovulation.

Indication: For use by females of reproductive potential to prevent pregnancy. Nextstellis® may be less effective in females with a BMI ≥30kg/m^2. In females with BMI ≥30kg/m^2, decreasing effectiveness may be associated with increasing BMI.

There is no pregnancy category for this medication; however, the risk summary indicates to discontinue Nextstellis® if pregnancy occurs, as there is no reason to use hormonal contraceptives during pregnancy. The use before menarche is not indicated.

Dosage Form: Blister card with 28 film-coated tablets in the following order:

- 24 pink active tablets containing 3mg drospirenone and 14.2mg estetrol
- 4 white inert tablets

Recommended Dosage: Start Nextstellis® using a day 1 start. Take one tablet by mouth at the same time every day with or without food. Refer to the prescribing information regarding additional administration instructions for starting in females with no current use of hormonal contraception or when switching to Nextstellis® from another contraceptive method, as well as when to start Nextstellis® after delivery and after abortion or miscarriage.

If vomiting or acute diarrhea occurs within 3 to 4 hours after taking an active tablet, take the new active tablet (scheduled for the next day) as soon as possible. Take the new tablet within 12 hours of the usual time of tablet-taking if possible. If more than 2 tablets are missed, follow the advice concerning missing tablets, including using backup non-hormonal contraception. For additional recommendations, refer to the prescribing information.

Drug Interactions: Avoid the concomitant use of Nextstellis® with strong CYP3A inducers. If concomitant use is unavoidable, use an alternative contraceptive method or backup non-hormonal contraceptive method during coadministration and up to 28 days after discontinuation of the strong CYP3A inducer. Use an alternative or backup contraceptive method during co-administration of Nextstellis® and moderate or weak CYP3A inducers and up to 28

days after discontinuation of the CYP3A inducer, unless the prescribing information of the specific inducer indicates there is no clinically significant interaction with Nextstellis®.

Consider monitoring serum potassium concentration in patients who take a strong CYP3A4 inhibitor long-term and concomitantly with Nextstellis®.

Separate the time of administration of Nextstellis® and drugs that may reduce the absorption of Nextstellis®.

Increase the frequency of glucose monitoring and increase anti-diabetic drug dosage, as needed, based on glucose levels if using Nextstellis® with anti-diabetic drugs, as concomitant use may reduce the blood glucose lowering effect of the anti-diabetic drugs.

Monitor serum potassium concentration in females at increased risk for hyperkalemia if take Nextstellis® concomitantly with drugs that may increase potassium concentration.

The concomitant use of Nextstellis® may decrease lamotrigine exposure, which may reduce the efficacy of lamotrigine. Adjust lamotrigine dosage as recommended.

Concomitant use of Nextstellis® with systemic corticosteroids may increase the exposure of certain systemic corticosteroids, which may increase the risk of corticosteroid-related adverse reactions. Consider more frequent monitoring for corticosteroid adverse reactions when used concomitantly with Nextstellis®.

Concomitant use of Nextstellis® may increase thyroid-binding globulin concentration. Monitor thyroid-stimulating hormone (TSH) level and follow the recommendation for thyroid hormone replacement per its prescribing information.

Box Warning: Nextstellis® has a box warning regarding cigarette smoking and serious cardiovascular events. Cigarette smoking increases the risk of serious cardiovascular events from combined hormonal contraceptive (CHC) use. This risk increases with age, especially in females over 35 years of age, and with the number of cigarettes smoked. For this reason, CHCs, including Nextstellis®, are contraindicated in females who are over 35 years of age and smoke.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Nextstellis®) in study C302. Please note that there was no placebo data in the prescribing information to compare with.* The most frequently reported adverse events included any adverse reaction (58.1%), mood disturbance (10.9%), bleeding irregularities (9.7%), breast symptoms (5.3%), headache (4.8%), dysmenorrhea (4.1%), weight increased (3.3%), acne (3.2%), and libido decreased/lost (1.3%).

Nextstellis® is contraindicated in females with conditions that predispose to hyperkalemia (e.g. renal or hepatic impairment, and adrenal insufficiency). Nextstellis® contains drospirenone, which has anti-mineralocorticoid activity, including the potential for hyperkalemia in high-risk females, comparable to a 25mg dose of spironolactone. Most females who developed hyperkalemia in the clinical development studies of Nextstellis® had only mild potassium elevations and/or isolated increases that returned to normal while still on study medication.

Monitor blood pressure periodically and stop Nextstellis® if blood pressure rises significantly. In addition, carefully monitor females with prediabetes and diabetes who are using Nextstellis®, as it may decrease glucose tolerance. And, consider alternative contraception for females with hypertriglyceridemia. Females with hypertriglyceridemia, or a family history thereof, may have an increase in serum triglyceride concentrations when using Nextstellis®, which may increase the risk of pancreatitis.

Studies suggest an increased risk of developing gallbladder disease among CHC users and use of CHCs may also worsen existing gallbladder disease.

Increase the dosage of thyroid hormone replacement therapy as needed in females taking Nextstellis®.

Females using Nextstellis® may experience unscheduled bleeding and spotting and may experience absence of scheduled bleeding, even if they are not pregnant.

Monitor females with a history of depression and discontinue Nextstellis® if depression recurs to a serious degree.

A causal relationship between the use of CHCs and the development of cervical cancer and intraepithelial neoplasia has not been clearly established. In observational studies, the use of oral hormonal contraceptives in females for 5 years or more, compared to females who did not use oral hormonal contraceptives, was associated with an increased risk of cervical cancer and intraepithelial neoplasia. In these studies, the use of oral hormonal contraceptives in females for 10 years or more, compared to females who received oral hormonal contraceptives for 5-9 years, was associated with an increased risk of cervical cancer and intraepithelial neoplasia.

Avoid Nextstellis® in females with hereditary angioedema. Exogenous estrogens may induce or exacerbate symptoms of hereditary angioedema.

Avoid Nextstellis® in females with a history of chloasma gravidarum or increased sensitivity to sun and/or ultraviolet radiation exposure. Chloasma may occur with Nextstellis® use, especially in females with a history of chloasma gravidarum.

Contraindications: In females who develop or are known to have the following conditions:

- A history of, increased risk for, or current arterial or venous thrombotic/thromboembolic disease. Examples include females who are known to
    - Smoke, if 35 years of age and older
    - Have current or history of deep vein thrombosis or pulmonary embolism
    - Have cerebrovascular disease
    - Have coronary artery disease
    - Have thrombogenic valvular or thrombogenic rhythm disease of the heart
    - Have inherited or acquired hypercoagulopathies
    - Have uncontrolled hypertension or hypertension with vascular disease
    - Have diabetes mellitus with hypertension or end-organ damage; or diabetes mellitus of >20 years duration
    - Have migraine headaches with aura
- Current or history of a hormonally-sensitive malignancy (e.g. breast cancer)
- Hepatic adenoma, hepatocellular carcinoma, acute hepatitis, or severe (decompensated) cirrhosis
- Use of hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations
- Abnormal uterine bleeding that has an undiagnosed etiology
- Renal impairment
- Adrenal insufficiency

Manufacturer: Mayne Pharma

Analysis: The efficacy of Nextstellis® was assessed in a prospective, multicenter, open-label, single-arm one-year study in North America that included 1,674 females between the ages of 16 to 35 years. The mean age of included patients was 25.8 years, the mean BMI was 25.8kg/m^2, and 70.1% were Caucasian. Females with a BMI between 30 and 35kg/m^2 accounted for 22.3% of the study population. Females with a BMI >35kg/m^2 were not enrolled in the study.

A total of 26 on-treatment pregnancies occurred in 1,524 females, contributing 12,763 at-risk cycles. The overall Pearl Index was 2.65 per 100 woman-years of use. The following table, adapted from the prescribing information, lists the Pearl Index (PI) by BMI subgroup. Note a trend of decreasing effectiveness with increasing BMI was observed in the study.

Subgroup	N	On-treatment pregnancies	At-risk cycles	Pearl Index
Study C302	1524	26	12,763	2.65
BMI (kg/m^2)				
<30	1187	20	10,113	2.57
≥30 to <35 ^	337	6	2,650	2.94

^ One female with a BMI of 48kg/m^2 was enrolled and included in the efficacy analysis

Place in Therapy: Nextstellis® is a combined hormonal contraceptive indicated for use by females of reproductive potential to prevent pregnancy. Nextstellis® may be less effective in females with a BMI ≥30kg/m^2. In females with BMI ≥30kg/m^2, decreasing effectiveness may be associated with increasing BMI. In an open-label, single-arm study, a total of 26 on-treatment pregnancies occurred in 1,524 females, contributing 12,763 at-risk cycles. The overall Pearl Index was 2.65 per 100 woman-years of use. A trend of decreasing effectiveness with increasing BMI was observed in this study. To provide some basis for comparison, another contraceptive method, the Annovera® vaginal ring that contains segesterone acetate and ethinyl estradiol, has an overall pooled unintended pregnancy rate (Pearl Index) of 2.98 per 100 woman-years[2] and condoms are generally cited as having a Pearl Index of 3-12[3].

There is no evidence at this time to support that Nextstellis® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Nextstellis® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Nextstellis [package insert]. Greenville, MC: Mayne Pharma, 2021.
[2] UpToDate online. Contraception: Hormonal contraceptive vaginal rings. Accessed June 2021.
[3] Pearl Index. Website: https://www.mdapp.co/pearl-index-calculator-244/. Accessed June 2021.