Drug Monograph

Drug Name: **Nextstellis® (drospirenone and estetrol) tablet**
Drug Class: **Estrogen and Progestin Combination Oral Contraceptive**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Nextstellis is available on a blister card of 28 film-coated tablets; 24 active tablets and 4 inert tablets. Each active tablet contains 3mg drospirenone and 14.2mg estetrol.
Manufacturer:	Distributed by: Mayne Pharma, Greenville, NC 27834.
Summary of Findings:	The efficiency of Nextstellis was established in a prospective, multicenter, open-label, single-arm, 1-year study in North America that enrolled 1674 female participants 16 to 35 years of age. In this study (Study C302) 28 on-treatment pregnancies were reported. Of those pregnancies, 26 of 28 occurred during the treatment period in subjects between 16 to 35 years of age, inclusive, at initial screening (ITT population). 1,524 subjects aged 16 to 35 years with at least 1 at-risk cycle in the study, reported 12,763 at-risk cycles. The Pearl Index was 2.65 per 100 women-years of treatment (95% CI: 1.73, 3.88). A trend of decreasing effectiveness with increasing BMI was observed in the study.

Status Recommendation:	☐ Clinical Edit ☒ Open Access	☐ PA Required ☐ PDL
Type of PA Criteria:	☐ Appropriate Indications ☒ No PA Required	☐ Non-Preferred ☐ Preferred

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Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

The CDC estimated that in 2017-2019, approximately 65% of women aged 15 to 49 years were currently using contraception. They also estimated that 76% of women aged 18 to 49 were at risk for unintended pregnancy and had ongoing or potential need for contraceptive services. Over the past several decades the options for contraception have significantly increased. These options include intrauterine devices (IUDs), hormonal methods (implants, injections, oral contraceptives, transdermal patches, and intravaginal rings), and barrier methods (diaphragms, condoms, caps, sponges, and spermicides). In addition to these methods, natural family planning methods such as fertility awareness, the withdrawal method, and the lactation amenorrhea method are used to prevent pregnancy. Despite the advancements in contraceptive methods available, oral contraceptive pills remain the most common reversible birth control method used among U.S. women aged 15 to 49 years.

Dosage Form [4]

Nextstellis consists of 28 oral tablets in a blister pack. The first 24 tablets are pink active tablets each containing drospirenone 3 mg and estetrol 14.2 mg and then four white inert tablets.

Manufacturer [4]

Distributed by: Mayne Pharma, Greenville, NC 27834.

Indication(s) [4]

Nextstellis is indicated for use in 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.

Clinical Efficacy [3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Combination hormonal contraceptives (CHCs) prevent pregnancy by suppressing ovulation. Drospirenone (DRSP) is a spironolactone analogue with anti-mineralocorticoid and antiadrogenic activity. Estetrol (E4) is a synthetic analogue of a natural estrogen synthesized by the fetal liver and present only during pregnancy. It is not metabolized to estradiol or estriol.

Pharmacokinetics:

	Estetrol (E4)	**Drospirenone (DRSP)**
Absorption	0.5 hours	1.0 hours

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Metabolism	Phase 2 metabolism to form glucuronide and sulphate conjugates which have negligible in-vitro estrogenic activity	CYP3A4; two main metabolites: acid form of DRSP generated by opening of lactone ring and the 4,5-dihydrodrospirenone formed by reduction followed by sulfation. Both metabolites are not pharmacologically active
Excretion	69% urine, 22% feces	38% urine, 44% feces
Half-life	27 hours	34 hours

Clinical Trials Experience:

STUDY 1 DESIGN (C302, NCT02817841)	Phase 3, prospective, multicenter, open-label, single-arm study (N=1524)
INCLUSION CRITERIA	• Heterosexually active female at risk for pregnancy and request ion contraception • Negative serum pregnancy test at enrollment • Aged 16 to 50 years inclusive at the time of signing of informed consent • Willing to use the investigational product as the primary method of contraception for 13 consecutive cycles • Body mass index ≤35.0 kg/m^2
EXCLUSION CRITERIA	• Menstrual cycle length shorter than 21 days or longer than 35 days • Smoking (or nicotine-containing products) if ≥35 years old • Increased risk for cardiovascular events including: dyslipoproteinemia requiring active treatment with antilipidemic agent; diabetes mellitus with vascular involvement; arterial hypertension with vascular involvement, etc. • Increased risk for venous thromboembolism including personal history of deep vein thrombosis (DVT) or pulmonary embolism (PE); known hypercoagulopathy, etc. • Undiagnosed abnormal vaginal bleeding • Hyperkalemia, or condition that predisposes to hyperkalemia • Presence or history of hormone-related malignancy • Renal or hepatic impairment • Concomitant use of medications known for potential for drug-drug interaction with study product
TREATMENT REGIMEN	Eligible subjects were to be treated with DRSP/E4 in a 24/4-day regimen (i.e., 24 active tablets followed by 4 inactive tablets) for up to a maximum of 13 consecutive cycles.
RESULTS	In Study C302, 28 on-treatment pregnancies were reported. Of those pregnancies, 26 of 28 occurred during the treatment period in subjects between 16 to 35 years of age, inclusive, at initial screening (ITT population). 1,524 subjects aged 16 to 35 years with at least 1 at-risk cycle in the study reported 12,763 at-risk cycles. The Pearl Index was 2.65 per 100 women-year (95% CI: 1.73, 3.88).
SAFETY	Discussed in the Adverse Effects section below.

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Contraindications [3,4]

- A history of, increased risk for, or current arterial or venous thrombotic diseases
    - 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 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

Warnings and Precautions [3,4]

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

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- Cervical Cancer: A causal relationship between the use of CHCs and the development of cervical cancer and intraepithelial neoplasia has not been clearly established.
- Hereditary Angioedema: Avoid Nextstellis in females with hereditary angioedema.
- Chloasma: Avoid Nextstellis in females with a history of chloasma gravidarum or increased sensitivity to sun and/or ultraviolet radiation exposure.

Adverse Effects [3,4]

Most common, ≥ 2%	(N=3632) %
Any adverse reaction	58.5
Mood disturbance	9.1
Bleeding irregularities	10.8
Breast symptoms	5.4
Headache	6.3
Dysmenorrhea	3.7
Weight increased	3.0
Acne	3.7
Libido decreased/lost	2.0

Drug Interactions [3,4]

Clinically significant drug interactions with other drugs that affect Nextstellis:

- CYP3A Inducers: Drospirenone (DRSP) is a CYP3A4 substrate. Concomitant use with strong CYP3A inducers or certain moderate or weak CYP3A inducers may decrease DRSP exposure which may then lead to contraceptive failure and/or increase breakthrough bleeding. Avoid concomitant use. If concomitant use is unavoidable, use an alternative contraceptive method (e.g., intrauterine device) or a back-up non-hormonal contraceptive method during co-administration and up to 28 days after discontinuation of the CYP3A inducer.
- Drugs that may reduce the absorption such as bile sequestrants may decrease the exposure of both estetrol (E4) and DRSP, which may lead to contraceptive failure and/or an increase in breakthrough bleeding. To prevent or manage, separate the time of administration of Nextstellis and the concomitant drug.

Clinically significant drug interactions of Nextstellis on other drugs:

- Anti-diabetic drugs: Nextstellis may reduce the blood glucose lowering effect of anti-diabetic drugs. To manage, increase frequency of glucose monitoring and increase anti-diabetic drug dosage as needed based on glucose levels.
- Drugs that may increase serum potassium concentration: Nextstellis has potential for an increase in serum potassium concentration when taken in combination with other drugs that may increase serum potassium concentration. To manage, monitor serum potassium concentration in females at increased risk for hyperkalemia.
- Lamotrigine: Nextstellis may decrease lamotrigine exposure which may reduce efficacy of lamotrigine. To manage, adjust lamotrigine dosage as recommended in its Prescribing Information based on Nextstellis initiation or discontinuation.
- Systemic corticosteroids: Nextstellis may increase the exposure of certain systemic corticosteroids, which may increase the risk of corticosteroid-related adverse reactions. To manage, follow the recommendation for the corticosteroid in accordance with its Prescribing Information and consider more frequent monitoring for corticosteroid adverse

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reactions during concomitant therapy with Nextstellis.

- Thyroid hormone replacement therapy: Nextstellis may increase thyroid-binding globulin concentration. To manage, monitor thyroid-stimulation hormone (TSH) level and follow the recommendation for thyroid replacement in accordance with its Prescribing Information.

Dosage and Administration [3,4]

- Starting Nextstellis using a Day 1 start. Take one tablet by mouth at the same time every day with or without food for 28 consecutive days.

Additional Administration Information:

Starting Nextstellis in females with no current use of hormonal contraception	• **Important:** • In females with irregular menstrual cycles, pregnancy testing may be necessary prior to initiation of Nextstellis • **Day 1 Start:** • Take the first pink active tablet on the first day of menses • Take subsequent pink active tablets once daily at the same time each day for a total of 24 days • Take one white inert tablet daily for 4 days and at the same time of day that active tablets were taken • Begin each subsequent 28-day pack on the same day of the week as the first cycle pack • If not starting on the first day of menses, use a non-hormonal contraceptive as back-up until one active tablet has been taken daily for 7 days in a row.
Switching to Nextstellis from another contraceptive method	**Start Nextstellis on the day:**
• Combined Oral Contraceptive (COC)	• When the new pack of the previous COC would have started
• Transdermal System	• When the next application would have been scheduled
• Vaginal Insert	• When the next insertion would have been scheduled
• Injection	• When the next injection would have been scheduled
• Intrauterine System	• After removal
• Implant	• After removal
• Progestin-only pill	• After the last tablet was taken
Starting Nextstellis after delivery (>20 weeks gestation)	Must not start earlier than 4 weeks after delivery (due to risk of thromboembolism). If menstrual cycles have not returned, consider possibility of ovulation and pregnancy and use additional nonhormonal contraception for the first 7 days of Nextstellis use.
Starting Nextstellis after abortion or miscarriage (≤14 weeks gestation)	Within the first 7 days of complete first trimester abortion or miscarriage, use additional nonhormonal contraception for the next 7 days. After the first 7 days, follow the instructions for

	"Starting Nextstellis in females with no current use of hormonal contraception".
>14 weeks but ≤20 weeks gestation	After 4 weeks following second trimester abortion or miscarriage. Consider duration of pregnancy and risk of thromboembolism. If menstrual cycles have not returned, consider possibility of ovulation and pregnancy and if not pregnant, use additional nonhormonal contraception for the first 7 days of Nextstellis use.

Instructions for Missed Doses:

• If one pink active tablet is missed	Take the missed tablet as soon as possible and take the next tablet at the scheduled time, even if two active tablets are taken in one day. Continue taking one tablet a day until the pack is finished.
• If two or more pink active tablets are missed in Week 1 or Week 2	Take one missed tablet as soon as possible and take the tablet for the current day (that means taking two tablets in one day) and discard the other missed tablets. Continue taking one tablet a day until the pack is finished. Use additional non-hormonal contraception as back-up until pink tablets have been taken for 7 consecutive days.
• If two pink active tablets are missed in Week 3	Take one missed tablet as soon as possible and take the tablet for the current day (that means taking two tablets in one day) and discard the other missed tablets. Finish the active tablets and discard the inactive tablets in the pack. Start a new pack of tablets the next day. Use additional non-hormonal contraception as back-up until pink tablets have been taken for 7 consecutive days.
• If one or more white inert tablets are missed	Skip the missed pill days and continue taking one tablet a day until the pack is finished.

Administration recommendations after vomiting or acute diarrhea:
If vomiting or acute diarrhea occurs within 3 to 4 hours of taking an active tablet, take the new active tablet schedule 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 two tablets are missed, follow the advice concerning missed tablets, including using back-up non-hormonal contraception.

Cost [(2)]

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Month
Estetrol/drospirenone tablets	Nextstellis®	Mayne Pharma	1 oral tablet daily	$190
Ethinyl estradiol and norethindrone acetate tablets	Lo Loestrin® Fe	Allergan	1 oral tablet daily	$168.50
Estradiol valerate and dienogest tablets	Natazia®	Bayer Healthcare Pharma	1 oral tablet daily	$246.41

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Ethinyl estradiol and drospirenone tablets	Yaz®	Various	1 oral tablet daily	$10.91

**Wholesale Acquisition Cost

Conclusion

In 2008, women reported that more than half of all pregnancies (51%) were unintended. Females aged 15 to 19 years reported that 75% of pregnancies were unintended. Due to these statistical findings, the United States set family planning goals in Healthy People 2020 to improve pregnancy planning and spacing, and to reduce the number of unintended pregnancies. These goals are to increase access to contraception that includes the full range of methods and to increase correct and consistent use of contraception for sexually active women. Over the last several decades, methods of contraception options have drastically increased.

Nextstellis is the first combined oral contraceptive to contain a combination of drospirenone and estetrol. In Study C302, 28 on-treatment pregnancies were reported. Of those pregnancies, 26 of 28 occurred during the treatment period in subjects between 16 to 35 years of age, inclusive, at initial screening (ITT population). 1,524 subjects aged 16 to 35 years with at least 1 at-risk cycle in the study reported 12,763 at-risk cycles. The Pearl Index was 2.65 per 100 women-year (95% CI: 1.73, 3.88). The drug has proven to be highly effective in this study, with an efficacy rate of ~98%, however there is limited available evidence whether Nextstellis has an improved safety profile over other available combination oral contraceptive options. Currently, Nextstellis carries a black box warning for serious cardiovascular events like other available combination oral contraceptives. The most common adverse reactions with Nextstellis use including bleeding irregularities, mood disturbance, headache, breast symptoms, dysmenorrhea, acne, weight gain, and decrease in libido.

Recommendation

MO HealthNet Division recommends Open Access status for this product.

References

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5) Mayne Pharma and Mithra announce FDA approval of new oral contraceptive Nextstellis. News release. Mayne Pharma Group Ltd; April 16, 2021. Accessed April 22, 2021. https://www.maynepharma.com/media/2506/fda-approval-of-noveloral-contraceptive-nextstellis.pdf

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