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Nextstellis® (drospirenone/estetrol): The Next Big Thing in Birth Control

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Although oral contraceptive pills (OCPs) are recognized as highly effective and generally safe, this method of contraception still carries remarkably low adherence rates. Numerous surveys show incorrect administration and a high discontinuation rate in as many as 60% of women[1-3]. This non-adherence is driven mostly by side effects (or simply the fear of them)[4]. According to the Center for Disease Control (CDC), 14% of women between the ages of 15 and 49 report using "the pill."[5] Most women report using OCPs to prevent pregnancy, although a significant amount (~ 15%) of women use OCPs to treat other health conditions such as irregular menstruation, menstrual pain, fibroids, acne, polycystic ovarian syndrome, endometriosis, and other related conditions.[6]

Currently, OCPs come in two varieties: the progestin only pills (POPs), and the combined oral contraceptives (COCs), which contain both an estrogen and a progestin component.[6] Combined oral contraceptives are by far the more commonly prescribed of the two, with POPs usually reserved for women who have a contraindication to the estrogen component of COCs, such as those who smoke over the age of 35, have a history of blood clots, or experience migraines with aura. POPs are also the preferred OCP in women who are breastfeeding due to the reduction in breastmilk caused by the estrogen component of COCs. The popularity of POPs has likely been curbed by their high rates of unpredictable bleeding and the tight 3-hour dosing window in which the patient must take their pill in order to achieve efficacy.[7] However, a newer POP, Slynd® (drospirenone 4mg), came to the market in June 2019, providing the first and only POP to offer a 24-hour missed pill window, comparable to COCs.[8,9]

In their time on the market, COCs have become infamous for their potential to cause nausea, breast tenderness, headaches, bloating, and mood disturbances. Results from a recent double-blind, randomized, controlled trial even suggests a popular COC (levonorgestrel and ethinyl estradiol) is associated with decreased general well-being, decreased self-control, and decreased vitality compared to placebo.[10]

Progress in developing new and improved COCs has historically centered around the progestin component, with several generations of progestins now available. Different progestins have allowed women and healthcare professionals to select their progestin component based on comparative effects of each progestin on lipid profiles, androgenic activity, acne, fluid retention, improvement in premenstrual dysphoric disorder (PMDD) symptoms, and other parameters. Progress in the estrogen component of COCs has lagged far behind that of its progestin counterparts with more than 97% of COCs containing ethinyl estradiol (EE).

In April of 2021, the FDA approved a new COC, Nextstellis®, containing the first new contraceptive estrogen in over 50 years.[4] This manuscript aims to discuss the pharmacology, adverse effects, precautions, and the potential place in therapy for Nextstellis®.

Pharmacology

Nextsellis® (DRSP/E4) is a monophasic combined oral contraceptive containing 3mg of DRSP and 14.2mg E4 of monohydrate. The main mechanism of COCs is to suppress ovulation by inhibiting gonadotropin-releasing hormone (GnRH) from the hypothalamus, inhibiting luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and disruption of the LH surge that occurs mid-cycle. These effects are achieved by both the estrogen and progestin components working in synchrony, but estrogen ability to suppress FHS and therefore prevent folliculogenesis, is likely the foundation of contraceptive efficacy in COCs. The progestin component of COCs contribute to contraceptive efficacy by causing decidualization and atrophy of the endometrium, thickening cervical mucus, and stunting ciliary actions in the fallopian tubes.[11]

Mechanism of Action

Estetrol (E4) is being touted as the first environmentally friendly estrogen. Endocrine-disrupting chemicals (EDCs) represent a considerable portion of the man-made contaminants in ground water and aquatic ecosystems, posing a health risk to wildlife and humans alike. E4 has undergone an Environmental Risk Assessment study in which its endocrine disruptive effects on the environment were insignificant in comparison to currently marketed estrogens.[12] E4 is also the first estrogen to be described as a

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Native Estrogen with Selective actions in Tissues (NEST)[13]. In humans, E4 is produced solely by the fetal liver and enters the maternal circulation through the placenta.[13] For clinical use, E4 is synthesized from plant-derived estrone.[14]

E4 is selective for tissues that predominantly depend on nuclear estrogen receptors. Tissues throughout the body respond differently to estrogen based on their dependence on nuclear or membrane receptor signaling.[13,15] Other contraceptive estrogens bind widely to two main types of estrogen receptor alpha: *nuclear* ER_{alpha} and *membrane* ER_{alpha}.[16,17] However, E4 activates nuclear ER_{alpha} while antagonizing membrane ER_{alpha}, giving it selective effects in different tissue types (**Figure 1**).[13-16] Due to the supposed prevention of cardiovascular plaque accumulation, maintenance of uterine and vaginal tissue, and lack of breast growth stimulation, some propose that E4 may provide an improvement in adverse drug reactions (ADRs) compared to currently existing estrogens. As with other estrogens used in COCs, E4's contraceptive properties are due to the ability to suppress FHS and therefore prevent folliculogenesis and ovulation.[17]

In contrast, but used in conjunction with E4, drosperinone (a derivative of spironolactone) is the only available fourth generation progestin. It is the only progestin that acts as an agonist at progesterone receptors (PR) while acting as an antagonist at both mineralocorticoid receptors (MR) and androgen receptors (AR).[19,20] The most important action of progesterone in the menstrual cycle is to prepare the endometrium for pregnancy. Exogenous contraceptive estrogens serve the opposite purpose, causing atrophy of the endometrium and the thickening of cervical mucus.[11] See **Table 1** for a comparison of currently available contraceptive progestins and associated estrogenic and androgenic properties.

Pharmacokinetics

E4 undergoes phase I metabolism by CYP3A4, and phase II metabolism by glucuronidation and sulfonation. In vitro studies show that UGT2B7 is the dominant UGT isoform that catalyzes the formation of E4-16-glucuronide. These conjugates have negligible in vitro estrogenic activity.[15] DRSP is metabolized initially by CYP3A4 to produce two main metabolites. One metabolite is the acid form of DRSP generated by opening of the lactone ring, while the other metabolite is formed by sulfation.[15] Additional pharmacokinetic parameters of E4 and DRSP are described in **Table 2.**

Figure 1 | Estrogenic Effects at ER_{alpha} Binding Sites[18]

Table 1 | Progestin Comparison Chart[16,22]

Generation	Progestin	Estrogen	Androgen	Anti-MR*
1st	Norethindrone	++	++	—
	Ethynodiol diacetate	++	+	
	Norgestreal	—	+++	
	Norethindrone acetate	++	++	
2nd	Levonorgestrel	—	++++	—
3rd	Norgestimate	—	++	—
	Desogestrel	+/-		
4th	Drospirenone	—	—	+

*Antimineralocorticoid

Clinical Trials

The FDA focused primarily on a single Phase III trial (C302) for Nextstellis® efficacy assessment, as it was conducted in the target population and was adequately sized and designed to provide evidence of effectiveness for the contraceptive product. Another trial conducted (C301) further supports the efficacy of Nextstellis®, but the population demographics were too dissimilar to the first trial, leading the FDA to exclude this study from the efficacy analysis for labeling purposes.[21] Details regarding Phase II and Phase III trials are noted below.

Phase II Studies Overview[21]

Four Phase II trials were completed, two of which were dose-finding studies, and two of which were primarily safety studies. The dose-finding studies compared two progestins, DRSP and levonorgestrel (LNG), in combination with E4 to find the most complementary progestin for E4, as well as its minimum effective dose. The Phase II trials, specifically addressing safety, directly studied Nextstellis® against Yaz® (20mcg EE/3mg DRSP) and Nordette® (30mcg EE/150mcg LNG), two commonly used COCs. Endpoints for the Phase II trials included effects on the inhibition of ovulation, bleeding patterns, sex hormone-binding globulin (SHBG), liver function tests, lipid and carbohydrate metabolism, hemostasis parameters and various endocrine parameters. No safety signals arose for Nextstellis® relative to the other COCs studied.[21] Study ES-C02 assessed the cycle control of DRSP/E4 3mg/14.2mg and LNG/E4 0.15mg/18.9mg in a 24/4 regimen for 6 cycles. DRSP/E4 3mg/14.2mg showed a lower incidence of unscheduled bleeding and the lowest incidence of an absence of withdrawal bleeding, leading researchers to choose DRSP as the most complimentary progestin to E4.[21]

E4 FREEDOM– North America (C302)

This Phase III, multicenter, open-label, single-arm trial aimed to evaluate the contraceptive efficacy and safety of Nextstellis®. The study enrolled 2,148 at 77 sites across North America with 1,864 starting in the investigational treatment arm. The demographic characteristics of the study subjects adequately reflect the population of American women seeking a COC, although non-White, overweight, and obese women were underrepresented compared to US population.

The study aimed to determine contraceptive efficacy for the women aged 16 - 35, but enrolled women 16 - 50 to be included in safety data. The key inclusion criteria were age 16 - 50, heterosexually active females with the potential of becoming pregnant and requesting contraception, and a BMI of less than or equal to <35.0 kg/m2. The main exclusion criteria were consistent with those of other trials evaluating COCs and included a baseline menstrual cycle shorter than 21 or longer than 35 days, increased

risk for CV events including VTE, renal or hepatic impairment, and a history of hormone-related malignancy. Because DRSP is a spironolactone derivative, hyperkalemia was another important exclusion criteria for this trial.[21]

Eligible subjects were treated with Nextstellis® (3mg DRSP/14.2mg E4) once daily in a 24/4-day regimen for up to 13 consecutive cycles. Participants were instructed to record their pill intake, sexual activity, use of any other contraceptive, and bleeding or spotting in a daily diary. Participants between the ages of 16 and 35 (1,524) contributed 12,763 at-risk cycles.

The primary efficacy endpoint was evaluated using the Pearl Index (PI), which is the most common method of determining contraceptive efficacy in clinical trials.[21] The PI represents the number of contraceptive failures per 100 women-years and is calculated by the following equation: PI = (number of unplanned pregnancies)/(number of cycles in which pregnancy could have occurred) x 1300. The lower the PI, the lower the risk of an unintentional pregnancy. As described in **Table 3**, the overall Pearl Index of this population was 2.65 per 100 women-year (95% CI: 1.73, 3.88). The Pearl Index was higher in black or African American women (6.80 vs. 1.77 in whites), subjects aged 25 or younger (3.07 vs. 2.13), BMI >30 kg/m2 (2.94 in subjects with a BMI of 30 - 35), and smokers (4.19 vs. 2.43).[17] **Table 4** depicts further subgroup analysis by racial subgroup and BMI.[21]

For the subjects that began treatment with Nextstellis®, 1,016 of 1,864 (54.5%) completed the study. The most common reasons for discontinuation were lost to follow-up (21.1%), consent withdrawal (10.0%), AEs not related to bleeding (6.3%), deviation from protocol (5.8%), and AEs related to bleeding (2.5%).

In terms of efficacy, Nextstellis® was found comparable to other available COCs with a PI of 2.65 (upper bound of 95% CI: 3.97).[21] In contrast, the PI of norethindrone/EE is 2.92 (UB of 95% CI: 4.21), of LNG/EE is 1.98 (UB 95% CI: 5.03), and of DRSP/EE 1.41 (UB 95% CI: 2.47).

E4 FREEDOM—European/Russian (C301)[17]

Although the efficacy data of this trial was not used for labeling purposes in the United States, the FDA included any adverse effects present in this study in their integrated safety analysis. The design, inclusion, and exclusion criteria were similar to those in Study C302 discussed above. Of the 1,553 subjects who began treatment with Nextstellis®, 1,218 (78.4%) completed the study. The demographic characteristics of subjects were dissimilar to those in the North American study arm, with the largest deviations being race (98.6% white vs. 70% other) and BMI (5.7% participants with BMI of 30 or greater vs. 23%). A total of 1,313 subjects contributed 13,692 at-risk cycles. The Pearl Index was 0.47 per 100 women-years (95% CI: 0.15, 1.11) with 2.6% participants lost to follow-up. Common adverse events (**Table 5**) were seen in both the North American and European/Russian trials.

Table 3 | Primary Endpoint by Subgroup Analysis for Subjects Aged 16 to 35 years (Study C302)[21]

Group	Pearl Index (95% CI)
All participants	2.65 (1.73-3.97)
Race	
White	1.77 (0.94-3.02)
Black or African American	6.80 (3.26-12.51)
Asian	4.28 (0.52-15.45)
Native American or Alaskan Native	——
Native Hawaiian or other Pacific Islander	——
Other	2.41 (0.06-13.44)
Age	
≥18 to ≤25	3.07 (1.68-5.14)
>25 to ≤35	2.29 (1.18-3.99)
Body Mass Index	
<25	2.43 (1.26-4.25)
≥25 to <30	2.81 (1.21-5.54)
≥30	2.94 (1.08-6.41)

Table 2 | Select Nextstellis® Pharmacokinetics[15]

Absorption	Estetrol (E4)	Drospirenone (DRSP)
T_{max}[a]	0.5-2 hour	1-3 hour
T_{ss}[b]	4 days	10 days
Distribution		
Protein Binding	46-50%	95-97% via albumin
Metabolism		
	None	CYP3A4
Elimination		
$T_{1/2}$[c]	27 hour	32 hour

[a]Time to maximum concentration; [b]Time to steady state; [c]Half-life

Adverse Effects

The most common adverse effects and rate of discontinuation seen with DRSP/E4 during clinical trials are similar to other CHC products. The amount of participants with unscheduled bleeding and the number of unscheduled bleeding days were also similar to other CHC products and dissipated as treatment continued.[21] All existing CHCs are associated with a known safety risk of thrombotic complications. During the study of DRSP/E4, two cases of deep venous thrombosis (DVT) occurred. One DVT occurred in a healthy White female in trial C302, and the other happened in a 54-year-old post-menopausal woman who was receiving five times the therapeutic dose of Nextstellis® in a Phase I safety study (not fully discussed here).[21] There is some epidemiological evidence to suggest DRSP containing CHCs have an increased risk for VTE above that associated with other progestins found in CHCs. A recent study found a hazard ratio of 1.6 when comparing users of EE/DRSP and EE/LNG.[32] For this reason, labeling with regard to potentially increased VTE risk were added to DRSP-containing containing products. With this in mind, there is insufficient data to determine the comparative thromboembolic risk between DRSP/E4 and other CHCs at this time.

A phenomenon unique to DRSP-containing CHCs is the risk of hyperkalemia. Although this risk is rare, in studying DRSP/E4 seven instances of elevated serum potassium occurred, none of which were associated with adverse events or symptoms.[21] DRSP/E4 may have less off-target endocrine effects than some other COCs. A significant increase in sex hormone binding globu-

Table 4 | Further Subgroup Analysis by Race and Body Mass Index for Subjects Aged 16 to 35 years (Study C302)[21]

Body Mass Index (baseline)	Racial Subgroup	Pearl Index (95% CI)
<30	White	1.35 (0.58-2.66)
	Black or African American	9.59 (4.60-16.63)
	Other*	2.48 (0.30-8.97)
≥30	White	3.49 (1.13-8.15)
	Black or African American	——
	Other*	5.53 (0.14-30.82)

*includes Asian, Native American or Alaskan, Pacific Islander and others

lin was observed with DRSP/EE, and was five times greater than that seen with DRSP/E4. DRSP/E4 also showed a significantly lower impact on decreasing DHEAs, with the impact of DRSP/EE being more than two-fold greater.[24]

Safety & Contraindications

Current FDA recommendations request assessment of all cardiovascular risk factors before starting DRSP/E4. Use is contraindicated in women with prior history or known active thromboembolism or pulmonary embolism, uncontrolled hypertension, those with a history of vascular disease, currently smoking nicotine containing products and over the age of 35, or suffer from a heart condition such as atrial fibrillation. Thrombotic events are more likely to occur in women over the age of 40, with hypertension, hyperlipidemia, diabetes, and/or smoke nicotine-containing substances.[17]

Discontinue use if new, recurrent, or severe migraines occur. Use in the setting of migraine with aura is currently contraindicated and recommendations include change to POP method.

Patients who have diabetes or who are at risk for developing diabetes should be monitored, as COCs may decrease glucose tolerance. Nextstellis® may increase triglycerides, which can increase the risk of pancreatitis in patients with preexisting hypertriglyceridemia.[21] Nextstellis® can also cause elevated liver enzymes and increase the risk of liver tumors. CHCs have been associated with an increased risk of developing or worsening gallbladder disease or cholestatic disease.[21] Use is contraindicated for those suffering from liver disease, such as hepatic adenoma, hepatocellular carcinoma, acute hepatitis or decompensated cirrhosis. Additional cautions exist in the setting of renal and adrenal insufficiency and use is not advised.

Precautions for Nextstellis® are similar for all currently available COCs (with the addition of hyperkalemia risk from the DRSP component).[21] DRSP anti-mineralocorticoid activity is comparable to a 25mg dose of spironolactone. In Phase III trials (n = 3,643), seven subjects developed hyperkalemia. Most cases presented only mild potassium elevation and/or isolated increases in potassium that returned to normal.[17] Patients taking other medications that may increase serum potassium levels should be monitored while taking Nextstellis® or any other DRSP containing COC.[17,21]

Lastly, data concerning the association of COCs with the onset of depression or exacerbation of existing depression is limited and somewhat conflicting. During clinical trials with Nextstellis®, one case of depression and one case of recurrent suicidal ideation that developed during treatment.[17] It is advisable to monitor patients with a history of depression or mood disorders in patients taking Nextstellis®.[21]

Dosage, Administration, & Cost

Nextstellis® tablets are available in a blister card. The 24 active tablets contain 3mg DRSP and 14.2mg E4. Nextstellis® uses a Day 1 start method, which requires the patient to take the first active tablet on the first day of their menstrual cycle. The patient should then continue to take the pink active tablets at the same time daily for 24 consecutive days. The following four days consist of white inert tablets.[17] The patient should then start the next 28-day pack. If the patient does not start on the first day of menses, a back-up form of contraception should be used until the active tablet has been taken correctly for one week.[17]

If one pink active tablet is missed, the tablet should be taken as soon as possible and the subsequent tablet should be taken as scheduled. If two or more pink active tablets are missed, take one missed tablet as soon as possible and take the tablet for the current day. Discard any other doses that were missed. Use back-up contraception until the pink tablets have been taken for seven consecutive days.[17] Incorrect administration may result in unintended pregnancy.

Table 5 | Common Adverse Effects with Nextstellis®

Adverse Effect	Incidence Rate
Bleeding	10.8%
Mood Disturbance	9.1%
Headache	6.3%
Breast Discomfort	5.4%
Acne	3.7%
Weight Increase	3.0%
Decrease in libido	2.0%

The average retail price for Nextstellis® is $232.23 per each 28-day blister pack.[25] Other COCs can be obtained through online subscription services for as low as $7 per month without prescription drug coverage, and several COCs are free on most major health insurances.[26-28] The cost of Nextstellis® will likely impact initial use.

Drug Interactions

DRSP is a CYP3A4 substrate. Use with CYP3A4 inducers may decrease exposure to DRSP, which may lead to contraceptive failure.[17] Use with CYP3A4 inhibitors may increase exposure to DRSP, which may lead to increased DRSP exposure and a higher risk of adverse events (particularly hyperkalemia).[17] Other medications that increase potassium may increase the risk of hyperkalemia when taking DRSP, and serum potassium should be monitored.[17,21]

Nextstellis® may decrease lamotrigine exposure when taking concomitantly and may increase exposure to systemic corticosteroids, which may increase the risk of the risk of adverse effects associated with corticosteroid use. The estetrol component of Nextstellis® may also increase thyroid-binding globulin concentration, necessitating an increase in thyroid replacement therapy for patients with hypothyroidism.[17]

Special Populations

Pregnancy & Breastfeeding

Nextstellis® should not be used during pregnancy and may be started no earlier than 4 weeks after delivery due to the increased thrombotic risk in the postpartum period.[17] The estrogen component of COCs can reduce milk production, making an alternate form of contraception favorable for most breastfeeding women.[18] If Nextstellis® is started during lactation, it should be done when breastfeeding is well established, as this reduces the risk of a decrease in milk supply.[17]

Renal & Hepatic Impairment

Nextstellis® is contraindicated in both renal and hepatic impairment. Renal impairment may increase the risk of hyperkalemia, as well as increase serum DRSP levels. Hepatic impairment also increases the serum levels of DRSP significantly.[17]

Patients with Higher Body Mass Index

The safety and efficacy of Nextstellis® in patients with a BMI

or 35 or greater has not been adequately studied. Given the results of trial C302, it appears the efficacy of Nextstellis® decreases as BMI increases.[21] There were not enough subjects enrolled in the higher BMI subgroups to support any definitive conclusions, and more studies involving overweight and obese patients must be conducted prior to recommendation for use.

Clinical Implications

Nextstellis® appears comparable to other COCs in efficacy and side effect profile. Based on the evidence presented in the new drug application (NDA) for Nextstellis®, the FDA determined there was no need to alter the general DRSP-containing COC package insert regarding adverse drug events (ADEs) for Nextstellis®. Additional large post-marketing studies need to be conducted to determine if Nextstellis® can be differentiated from other COCs in terms of its safety and side effect profile. Trial C302 performed a subgroup analysis of efficacy in patients in different races, BMIs, and ages. Calculated PIs for the higher BMI and Black or African American subgroups, were higher than averages from the trial. These subgroup analyses were intended to be exploratory in nature, and sample sizes for the subgroup analyses were small, and produced large confidence intervals.[21] Larger post-marketing subgroup analyses are needed further investigate these trends. Decreased efficacy of hormonal contraceptives in overweight and obese women is not exclusive to DRSP/E429.

As previously stated, E4 is an agonist at nuclear dependent ER_{alpha} receptors and an antagonist at membrane dependent ER_{alpha} receptors. Nuclear dependent ER_{alpha} activation retains the benefit of bone mineral density maintenance seen in less selective estrogens.[13] Selective nuclear ER_{alpha} activation is being sold as a way to improve the safety and side effect profile of COCs, however, this data has come solely from in vitro and animal studies. Whether these proposed benefits make a clinical difference in the adverse effects, has yet to be sufficiently proven in human subjects. Post-marketing studies and real-world data gathered after the release of DRSP/E4 will likely help clarify benefit. If it does demonstrate the cardiovascular and reproductive tissue benefits that are proposed, we may see a shift farther from EE in favor of E4.

Given the cost and lack of identifiable clinical differences in the efficacy, adverse effects, or safety profiles observed during clinical trials, the integration of DRSP/E4 will likely be a slow one. However, the approval of E4 as a contraceptive estrogen, has created its own class, NEST, which opens the doors for further manipulation of the estrogen component of COCs.

Conclusion

E4 is the first estrogen to be approved by the FDA in five decades and is the first of the class NEST. In vivo animal studies have demonstrated that in comparison to previous contraceptive estrogens, E4 has different actions and selectivity at estrogen receptors, leading investigators to believe it may have an improved safety and adverse effects profile.[13] Clinical trials spanned 13 menstrual cycles (approximately 1 year), during which DRSP/E4 was found to be comparable to other COCs.[21] Though DRSP/E4 provides an additional OCP option, efficacy appears to decline as BMI increases. Large post-marketing surveillance will be needed to discern whether Nextstellis® truly provides the improved side effect and safety profiles its mechanism proposes.

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