

Company

Mayne Pharma

Drug or Device Name

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

Category

Pharmaceutical

Compound/Technical Name

drospirenone 3 mg/estetrol 14.2 mg

Trade Name

Nextstellis

Date of Approval

04/15/2021

Therapeutic Categories

Women's Health Contraception Combined Oral Contraceptive Pill

Indications

Nextstellis® is a combination of estetrol (E4), an estrogen, and drospirenone, a progestin, indicated for use by females of reproductive potential to prevent pregnancy. With its unique pharmacologic profile, scientific interest in E4, the estrogen in NEXTSTELLIS, is high. E4 is being evaluated in other therapeutic domains, such as hormone therapy during menopause and advanced breast cancer, advanced prostate cancer, as well as in neuroprotection.

Background

Combined oral contraceptive pills (COC), introduced in the 1960s, are the most popular contraceptives in the U.S. and are widely used globally. COCs contain both estrogenic and progestational components. The progestin primarily prevents pregnancy by disrupting gonadotrophin secretion, thereby inhibiting ovulation. The estrogen primarily balances the progestin's effects on the endometrium, thereby providing endometrial support and an acceptable bleeding pattern. Since the 1960s, efforts have been focused on developing new progestins to improve COC safety and tolerability. The androgenicity of early progestins had adverse metabolic impacts (e.g., insulin resistance, increased lipids) as well as other side effects (e.g., weight gain, hirsutism, acne, oily hair, seborrhea). Now, several less androgenic and anti-androgenic progestins are available. Only three estrogens have been previously used in COCs: First was mestranol, rapidly replaced by ethinyl estradiol (EE). Estradiol valerate (E2V) was introduced in one COC in 2010. However, ~99% of COCs used today contain EE. Shortly after being introduced, COCs were associated with an increased risk of venous thromboembolism (VTE). The EE dose, identified as the main contributor to this risk, was reduced over time from >100 to 10 mcg. This decreased VTE incidence, but it also resulted in less acceptable bleeding profiles. Despite these advancements, COCs still have many side-effects, including some rare but serious thrombotic effects. Epidemiological studies show an increased VTE incidence with formulations that incorporate less androgenic progestins, even with low EE doses, presumably due to the higher estrogenicity of these combinations. COCs containing EE also impact many metabolic, endocrine, and hemostatic biomarkers. EE is extensively metabolized by the liver, and EE can stimulate growth of malignant breast cells, if present. Until now, women have had very limited choices regarding the type of estrogen in their COC. There has been an unmet need for an estrogen that provides the estrogen benefits women want in a COC, but with an improved safety and tolerability profile.

Development

Estetrol (E4) is a human estrogen, produced only during pregnancy by the fetal liver, and it is now made from a plant source. It was discovered at the Karolinska Institute in 1965. Studies evaluating E4's potential for therapeutic use began in 2000, when extensive pre-clinical work to understand its properties started. Beginning in 2009 until today, Mithra Pharmaceuticals has been at the forefront of E4 development. This work has demonstrated the unique pharmacokinetic and pharmacodynamic profile of E4, including its effectiveness for ovulation inhibition, while having minimal effects on liver protein synthesis and liver metabolism, as well as a low impact on hemostatic parameters. E4 showed selective estrogenic effects in tissues where desirable (e.g., endometrium, vagina, bone, vasculature) with minimal impact on tissues where it is undesirable (e.g., breast, liver). E4 showed promise to be a superior estrogen for efficacy in a COC with a potentially better safety profile. E4, as well as its properties when combined with DRSP, is what makes NEXTSTELLIS significantly different from other COCs. Drospirenone (DRSP) is a well-known progestin that was originally approved in Yasmin® (DRSP/EE) in 2001. It has anti-estrogenic and anti-mineralocorticoid activity. Four Phase 2 studies were conducted with E4, all with various standard-of-care comparators, including YAZ® (DRSP/EE) and Nordette® (levonorgestrel/EE), and Natazia® (dienogest/E2V). Two studies were to determine optimal E4 dose and to select a progestin, and two studies were to assess the pharmacodynamics of the E4/DRSP combination (NEXTSTELLIS). These studies measured impact on endocrine, metabolic, and hemostatic biomarkers, ovulation inhibition, and bleeding profiles. Two large (n=3,632), year-long, Phase 3 studies were conducted. The North American study included a diverse patient population, with a wide range of

ages (16-50 years), BMI (23% were 30-35 kg/m²), ethnicities, and contraceptive use history. E4 is currently being investigated in several other therapeutic domains, including some cancers.

Innovation

Because E4 is natural and well-tolerated in high concentrations during pregnancy by both mother and fetus, it was an attractive candidate for use in a COC. The ability to produce large quantities of E4 from plants is a major innovation. More than 20 years of clinical research have led to a new COC based on E4 (NEXTSTELLIS), which incorporates this new estrogen that has never before been used in any medicine. Synthetic estradiol-based estrogens that are incorporated in COCs other than NEXTSTELLIS have potent, widespread effects throughout a woman's body. NEXTSTELLIS is the first COC to contain a native, selective estrogen with deliberate tissue-specific effects. Until now, women choosing a COC have had to make a compromise: Sufficient estrogen exposure for good cycle control, but with significant safety and tolerability trade-offs. With the innovation of E4 and NEXTSTELLIS, women can have a COC that averts this need to compromise. E4 has many unique properties: • Pharmacological properties different from other estrogens: - Long half-life (24-28 hours) - Minimal impact on liver proteins, including sex hormone binding globulin (SHBG), hemostatic parameters, lipids, and glucose - No significant impact on CYP enzymes, minimizing the risk of drug-drug interactions • Distinct mode of action. Considered the first Native Estrogen with Selective Action in Tissues (NEST): - Supports endometrium, vagina, bone, and vascular system - In the presence of estradiol, E4 acts as an estrogen antagonist on normal and malignant breast cells - Liver neutral impact Based on Phase 2 studies, DRSP was selected as the best partner for E4: • Anti-androgenic and anti-mineralocorticoid properties • Pharmacologically similar to natural progesterone. Based on clinical studies, NEXTSTELLIS provides: • Excellent contraceptive efficacy • Predictable, favorable bleeding profile • Low impact on metabolic, endocrine, and hemostatic parameters • Favorable safety profile, with a low rate of VTE • Good tolerability with low rates of common side effects (e.g., weight gain, acne, headache, mood disturbance, loss of libido). In conclusion, as the first NEST, E4 has the potential to initiate a new era in COC safety and tolerability for the first time in 60 years.

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Attachments

- 1656439016Klipping_et_al._Contraception_April_2021_Endocrine_and_Metabolic_Parameters_of_New_OC_with_estetrol_and_DRSP.pdf
- 1656438731Gerard_C_et_al._Profile_of_estetrol_a_promising_native_estrogen.pdf
- 1656438569References_for_Prix_Galien_submission_with_article_titles_and_PubMed_links.docx
- 1655924433Joint_Press_Release_FDA_approval_April_16_2021_final.pdf
- 1656359399North_American_Phase_3_study_publication_Contraception_August_2021.pdf
- 1656440190Fruzzetti_F_et_al._Estetrol_a_new_choice_for_contraception_J_Clin_Med_2021_E4_COC_Review_(003)_clean_copy_no_highlights.pdf

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