APPLICATION NUMBER:

214154Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
<table>
<thead>
<tr>
<th><strong>Application Type</strong></th>
<th>NDA</th>
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<tr>
<td><strong>Application Number</strong></td>
<td>214154</td>
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<tr>
<td><strong>PDUFA Goal Date</strong></td>
<td>April 15, 2021</td>
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<td><strong>OSE RCM #</strong></td>
<td>2020-804</td>
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<tr>
<td><strong>Reviewer Name(s)</strong></td>
<td>Theresa Ng, PharmD, BCPS</td>
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<tr>
<td><strong>Team Leader</strong></td>
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<tr>
<td><strong>Review Completion Date</strong></td>
<td>March 22, 2021</td>
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<tr>
<td><strong>Subject</strong></td>
<td>Evaluation of Need for a REMS</td>
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<tr>
<td><strong>Established Name</strong></td>
<td>Drospirenone (DRSP)/ Estetrol monohydrate (E4)</td>
</tr>
<tr>
<td><strong>Trade Name</strong></td>
<td>Nextstellis</td>
</tr>
<tr>
<td><strong>Name of Applicant</strong></td>
<td>Mayne Pharma LLC</td>
</tr>
<tr>
<td><strong>Therapeutic Class</strong></td>
<td>Progestin and estrogen combination hormonal contraceptive (CHC)</td>
</tr>
<tr>
<td><strong>Formulation(s)</strong></td>
<td>Drospirenone/ Estetrol monohydrate or E4 (DRSP/E4) is supplied in blister cards, each containing 24 film-coated pink tablets and 4 round, film-coated white tablets. Each pick tablet contains 3 mg drospirenone (DRSP) and 15 mg estetrol monohydrate (E4) (equivalent to 14.2 mg estetrol). Each white tablet is inert placebo and does not contain DRSP and E4.</td>
</tr>
<tr>
<td><strong>Dosing Regimen</strong></td>
<td>One tablet daily orally as directed on the blister pack.</td>
</tr>
</tbody>
</table>
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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Nextstellis (drospirenone/ estetrol monohydrate or E4 [DRSP/ E4]) is necessary to ensure the benefits outweigh its risks. Mayne Pharma LLC (Mayne) submitted a New Drug Application (NDA) 214154 for Nextstellis proposed for use by females of reproductive age to prevent pregnancy. The risks associated with Nextstellis include venous thrombotic events (VTEs), and serious cardiovascular events in women who are over 35 years of age and smoke cigarettes. The Applicant did not submit a proposed REMS or risk management plan with this application.

DRM has determined that a REMS is not needed to ensure the benefits of Nextstellis outweigh its risks. Nextstellis demonstrated efficacy in prevention of pregnancy for the targeted population and is similar in efficacy and safety to currently approved combination hormonal contraceptives (CHCs). Nextstellis, like all currently approved CHCs, will use professional labeling to communicate the risks of VTEs and serious cardiovascular events.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Nextstellis (Drospirenone (DRSP)/ Estetrol monohydrate (E4), henceforth referred to as DRSP/E4, is necessary to ensure the benefits outweigh its risks. Mayne Pharma LLC (Mayne) submitted a New Drug Application (NDA) 214154 for Nextstellis with the proposed indication to prevent pregnancy in females of reproductive age. This application is under review in the Division of Urology, Obstetrics, and Gynecology (DUOG). The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Nextstellis is a new oral monophasic combination hormonal contraceptive (CHC) containing 3 mg of drospirenone (DRSP) and 15 mg of estetrol monohydrate also known as E4 (equivalent to 14.2 mg estetrol). E4, the estrogen component of the Nextstellis, is considered a new molecular entity (NME). E4 is a synthetic analogue of a native human estrogen produced by the human fetal liver during pregnancy with weaker estrogen properties compared to estradiol (E2) and ethinyl estradiol (EE). DRSP is a progestogen derived from spironolactone with anti-mineralocorticoid activity, but with no biologically relevant androgenic, estrogenic, glucocorticoid, or anti-glucocorticoid activity. There are two United States (US) approved CHCs containing the components of DRSP/ EE. These are Yasmin® (NDA 21098 [DRSP/ EE 3 mg/ 0.3]), approved in 2001 and Yaz® (NDA 21676 [DRSP/ EE 3 mg/ 0.20]), approved in 2006. Nextstellis was submitted as a 505(b)(2) application relying on the efficacy and safety data of DRSP in Yaz®.

References

Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.
CHCs prevent pregnancy by suppressing ovulation. DRSP, the progestogen component of Nextstellis, prevents pregnancy by inhibiting ovulation primarily via central feedback mechanism resulting in decreased luteinizing hormone secretion by the pituitary and makes the cervical mucus inhospitable to sperm. E4, the estrogen component of Nextstellis, contributes to contraceptive efficacy because of its inhibitory effect on follicle stimulating hormone secretion and stabilizes the endometrium (in balance with progestin) to provide an acceptable cycle control and bleeding pattern.

Nextstellis is proposed to be supplied in a blister pack composed of 3 mg DRSP and 15 mg E4 in a fixed dose tablet for patients to take at home. The proposed treatment regimen consists of one DRSP/ E4 3/15 mg tablet taken orally daily for 24 days followed by one placebo tablet taken orally daily for 4 days (24/4 day regimen). The CHC class has a boxed warning (BW) for increased risk of cardiovascular adverse events in patients, particularly in females over 35 years old, who use CHCs and smoke cigarettes. Nextstellis is not currently approved in any jurisdiction.

2.2 Regulatory History
The following is a summary of the regulatory history for NDA 214154 relevant to this review:

- 09/25/2020: The Agency conducted a Mid-cycle meeting (MCM) with the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no risk management issues at this time for Nextstellis.
- 1/14/2021: The Agency held a Late Cycle meeting with the Applicant via teleconference. The Agency informed the Applicant of the requirement for a Postmarketing Requirement (PMR) for an observational cohort study comparing the risks for fatal and non-fatal VTE and ATE in new users of NEXTSTELLIS and comparator combined hormonal contraceptives for contraception.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition
Progestin and estrogen combination hormonal contraceptives (CHCs) are widely used in the US and elsewhere for pregnancy prevention. CHCs are highly effective contraceptives and have several non-contraceptive benefits in the management of endometriosis, headaches, and acne. In the US, data from the National Survey of Family Growth from 2015-2019 estimated that 65.3% of women aged 15-49 used contraception with 14% using the oral contraceptive pill.

3.2 Description of Current Treatment Options
Multiple options for CHC tablets in mono, bi, and tri-phasic formulations of different strengths of progestin/estrogen combinations are available. Additional contraceptive formulations include transdermal patches, injectables, vaginal rings, subdermal implants and intrauterine (IUD) devices. DRSP is approved in the US in combination with EE or alone in several contraceptive products. These

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b Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.
products include: Yasmin® NDA 21098 (containing 3 mg DRSP/0.30 mg EE), and Yaz® NDA 21676 (containing 3 mg DRSP/0.20 mg EE) and at a higher dose drospirenone-only birth control pill, Slynd® NDA 211367 (4 mg daily). See table 1 for listing of available CHC containing DRSP. This application utilizes YAZ® as a reference to bridge the DRSP component of Nextstelis.

Table 1. Selected oral contraceptive including drospirenone alone and in combination with estrogen

<table>
<thead>
<tr>
<th>Products</th>
<th>Progestin component</th>
<th>Estrogen component</th>
<th>Selected Risk Mitigation Approaches in labeling:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Boxed Warnings (BW)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Warnings and Precautions (W&amp;P)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Medication Guide (MG)</td>
</tr>
<tr>
<td>Monophasic Combination</td>
<td></td>
<td></td>
<td>BW:</td>
</tr>
<tr>
<td>Beyaz 28</td>
<td>Drospirenone 3 mg</td>
<td>Ethinyl estradiol</td>
<td>• Cigarette smoking and serious cardiovascular events</td>
</tr>
<tr>
<td>Glanvi 28</td>
<td></td>
<td>0.20 mg</td>
<td>W&amp;P:</td>
</tr>
<tr>
<td>Loryna 28</td>
<td></td>
<td></td>
<td>• Vascular risks</td>
</tr>
<tr>
<td>Nikki 28</td>
<td></td>
<td></td>
<td>• Hyperkalemia</td>
</tr>
<tr>
<td>Yaz</td>
<td></td>
<td></td>
<td>• Liver Disease</td>
</tr>
<tr>
<td>Ocella 28</td>
<td>Drospirenone 3 mg</td>
<td>Ethinyl estradiol</td>
<td>• High blood pressure</td>
</tr>
<tr>
<td>Safyra 28</td>
<td></td>
<td>0.30 mg</td>
<td>MG available</td>
</tr>
<tr>
<td>Tydemy 28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yasmin 28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zarah 28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progestin-only</td>
<td>Drospirenone 4 mg</td>
<td>None</td>
<td>W&amp;P:</td>
</tr>
<tr>
<td>Slynd</td>
<td></td>
<td></td>
<td>• Hyperkalemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Thromboembolic disorder</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Bone loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Liver disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MG available</td>
</tr>
</tbody>
</table>

Use of CHCs increases the risk of cardiovascular events and cerebrovascular events, such as myocardial infarction and strokes. The risk increases with age, particularly in females 35 years of age and older, and with the number of cigarettes smoked. CHC use also increases the risk of venous thromboembolic events (VTEs), such as deep vein thrombosis (DVT) and pulmonary embolism (PE). The rate of VTE in females on CHCs has been estimated to be 3 to 9 cases per 10,000 woman-years. Risk factors for VTEs include smoking, obesity, family history of VTE, and prolonged immobilization. The risk of VTE is highest during the first year of CHC use and when restarting hormonal contraception after a break of four weeks or longer. The risk of VTE returns to baseline approximately 3 months after CHC use is discontinued.

The effect of CHCs on the risk of thrombosis is thought to be due to estrogen’s effect on hepatic synthesis functions, which leads to an increased production of several proteins involved in the coagulation and inflammatory pathways. Given the popularity and widespread use of CHCs, any increase in the relative risk of VTE for particular CHC formulations could translate to an excess absolute risk of important magnitude. The Applicant proposes Nextstelis as an effective low estrogenic/progestin CHC option.
4 Benefit Assessment

The Applicant submitted two pivotal phase 3 trials: MIT-C301 (C301, NCT02817828) conducted in Europe and Russia, and MIT-C302 (C302, NCT02817841) conducted in US and Canada to support the efficacy and safety of DRSP/E4 to prevent pregnancy in women. Due to differences in the study populations with higher obesity rates in the US than in the European population, demographics, and compliance history, the review team will primarily focus on the efficacy and safety results from Study C302 (US/Canada) for approval; the efficacy and safety results from Study C301 (Europe/Russia) are considered supportive. Pooled data from the two phase 3 studies and three phase 2 studies (MIT-C201, IT-C202, and ES-C02) are included to support the safety of DRSP/E4. In addition, the Applicant submitted Study MIT C112, a bridging study, to show compatibilities in the DRSP component in YAZ® (DRSP/EE 3/0.02 mg), the reference listed drug (RLD), and DRSP/E4.

Both phase 3 studies (C301 and C302) were multicenter, open-label, single-arm studies to evaluate the contraceptive efficacy and safety of DRSP/E4. The duration of treatment was 13 consecutive 28-day cycles. Study C301 included females 18 to 50 years old while Study C302 include females 16 to 35 years old.

The primary endpoint for both phase 3 studies was the number of on-treatment pregnancies as assessed by the Pearl Index (PI) in the intention-to-treat (ITT) population (16 to 35 years old), inclusive, at the time of screening with at-risk cycles.

The secondary endpoints were:

- The number of on-treatment pregnancies assessed by the Pearl Index based on at-risk cycles for all subjects in the ITT Population.
- The number of on-treatment pregnancies assessed by the Pearl Index based on all cycles for subjects aged 16 to 35 years and all subjects in the ITT Population, respectively.
- The cumulative pregnancy rate estimated by the life-table method based on all cycles for subjects aged 16 to 35 years and all subjects in the ITT Population, respectively.

The phase 3 studies enrolled 2148 (1864 ITT) in Study C301 and 1577 subjects (1553 ITT) in Study C302.

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On-treatment pregnancies were defined as pregnancies with an estimated date of conception between the date of first dose of study medication and 2 days (for C301) and 7 days (for C302) after the last dose of study medication (inclusive) for contraceptive efficacy.

Pearl Index (PI) is a statistical estimation of contraceptive efficacy and is expressed as the number of on-treatment pregnancies pregnancy per 100-woman of exposure; a high PI indicates high chance of unintentional pregnancy and low value represents low chance of pregnancy. Per US Guidance for combined hormonal contraceptives (Draft Guidance for Industry Contraceptives, 2019), combined hormonal contraceptives are very effective at preventing pregnancy, typically having an upper bound of this 95% confidence interval below 5 in adequately designed and conducted trials.

At-risk cycle: cycles in which no other methods of birth control [including condoms and emergency contraception] and during which the subjects confirmed that sexual intercourse had occurred.
Both phase 3 studies (C301 and C302) demonstrated contraceptive efficacy for the primary endpoint of on-treatment pregnancies. Per the 2019 US Draft Guidance for Industry Establishing Effectiveness and Safety for Hormonal Drug Products Intended to Prevent Pregnancy, CHC are considered effective at preventing pregnancy in adequately designed and conducted trials, typically, with an upper bound of the 95% confidence interval of the PI estimate below 5. In Study C301, there were 5 on-treatment pregnancies, leading to a PI of 0.47 per 100 women-year (95% CI: (0.15, 1.11)); in Study C302, there were 26 on-treatment pregnancies, leading to a PI of 2.65 per 100 women-year (95% CI: 1.73, 3.88). The overall PI from the pooled analysis was 1.52 per 100 woman-year (95% CI: 1.04, 2.16).

Secondary endpoint results for on-treatment pregnancies assessed by at-risk cycles and all cycles from both studies were within acceptable PIs and CIs and support the primary endpoint.

The life-table estimates of the cumulative pregnancy rate after 13-cycle of use for the two phase 3 studies are summarized below:

- **Study C301:**
  - subjects aged 18 to 35 years: 0.45% (95% CI: 0.19%, 1.09%)
  - all subjects in the ITT Population: 0.39% (95% CI: 0.16%, 0.94%)

- **Study C302:**
  - subjects aged 16 to 35 years: 2.07% (95% CI: 1.40%, 3.05%)
  - all subjects in the ITT population: 2.00% (95% CI: 1.38%, 2.91%)

The review team assessed the subgroup analysis by race, age, BMI, hormonal contraceptive use, and smoking status at baseline in Study C302 (US/Canada). Of note, the PI for subjects aged 16 to 35 was numerically higher in Black or African American subjects, and slightly higher in subjects aged 25 years or younger, BMI ≥ 30, hormonal contraceptive starters, and smokers. Further analysis by BMI showed decreasing effectiveness with increasing BMI as shown in Table 5.

### Table 5 Pearl Index Based on At-Risk Cycles and Reported Pregnancies in Females ≤ 35 Years of Age in Study C302

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>On-treatment pregnancies</th>
<th>At-risk cycles</th>
<th>Pearl Index (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study C302 – Modified ITT*</td>
<td>1524</td>
<td>26</td>
<td>12,763</td>
<td>2.65 (1.73, 3.88)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>1,187</td>
<td>20</td>
<td>10,113</td>
<td>2.57 (1.57, 3.97)</td>
</tr>
<tr>
<td>≥ 30</td>
<td>337</td>
<td>6</td>
<td>2,650</td>
<td>2.94 (1.08, 6.41)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td>742</td>
<td>12</td>
<td>6,416</td>
<td>2.43 (1.26, 4.25)</td>
</tr>
<tr>
<td>≥ 25 to &lt; 30</td>
<td>445</td>
<td>8</td>
<td>3,697</td>
<td>2.81 (1.21, 5.54)</td>
</tr>
<tr>
<td>≥ 30</td>
<td>337</td>
<td>6</td>
<td>2,650</td>
<td>2.94 (1.08, 6.41)</td>
</tr>
</tbody>
</table>

*Modified ITT includes all subjects ages 16-35 with at least 1 at-risk cycle


Study C302 excluded subjects with BMI ≥ 35 kg/m². The clinical reviewer noted the subgroup analysis results were exploratory, based on a limited number of subjects and at-risk cycles observed in the study and should be interpreted cautiously. There were high cumulative drop-out rates in Black or African American subjects and those with BMI ≥ 30 kg/m². The PI observed in the study may not fully represent...
the actual efficacy of the study drug in the targeted patient population. Although Study C301 subgroup analysis also showed higher PI for Black or African Americans and smokers, no meaningful comparison can be made due to low enrollments.

As required for the 505(b)(2) pathway, the DRSP exposure provided by DRSP/E4 and the listed reference drug, YAZ®, was investigated in a comparative bioavailability study (Study MIT-Es001-C112). This study showed that the rate and extent of DRSP exposure following a single oral administration of the to be marketed DRSP/E4 combination was comparable to YAZ®.

The bleeding patterns assessed using patient diaries in Studies C301 and C302 were characterized by predictable withdrawal bleeds with low occurrences of bleeding irregularities. In Studies C301 and C302, a total of 54 and 48 women (3.4% and 2.6%), respectively, discontinued from these studies of DRSP/E4 due to problems with irregular bleeding or amenorrhea. The clinical reviewer concurred with this finding.

Overall, the clinical reviewer determined Study C302 adequately represented the US population to draw conclusion regarding the effectiveness of DRSP/E4 and concluded the contraceptive efficacy of DRSP/E4 is acceptable for approval. The higher rates of drop-outs for those with BMI > 30 kg/m² and the restriction against enrollment of subjects with BMI > 35 kg/m² in DRSP/E4 clinical development program limited comparisons of contraceptive efficacy based on BMI subgroups. The clinical reviewer noted that given concerns regarding potentially reduced effectiveness of CHC in overweight or obese individuals, further study may be warranted in females of reproductive potential with BMI ≥ 30 kg/m² seeking contraception (see section 8).

5 Risk Assessment & Safe-Use Conditions

The Applicant submitted an Integrated Safety Summary (ISS) consisting of data from the two phase 3 studies (C301 and C302) and three phase 2 studies (MIT-C201 [NCT02957630], MIT-C202 [NCT03091595], and ES-C02[NCT02817828]) to support the safety of DRSP/ E4 3/15 mg. Additional information from a phase 1 study, MIT-Es0001-C106 (NCT03512860), is reported for thrombosis event. The safety population included all subjects who received at least one dose of the investigational product (or comparator) and included subjects who were treated with at least one dose of the DRSP/E4 as recorded in the subject diary (N=3,575), plus, subjects who were dispensed pills, but for whom there was no pill intake record showing treatment in the subject diary, or return of the dispensed pills in the drug accountability (N=215). A total of 2,212 participants completed 13 cycles of treatment in the two phase 3 trials, contributing a total of 35,677 cycles of exposure for the safety analysis. The mean time of DRSP/E4 exposure was 317 and 257 days for the respective studies (C301 and C302). The safety profile was similar to other drospirenone/ estrogen CHC including commonly reported (> 2%) adverse events (AEs) of headache (6.8%), metrorrhagia (4.6%), acne (3.9%), dysmenorrhea (3.5%), vaginal hemorrhage 3.1%), nausea (2.8%), weight increased (2.7%), breast pain (2.3%), and abdominal pain (2.2%). The most frequent adverse reaction leading to study drug discontinuation was bleeding irregularity (2.8%).

Reference ID: 4766006
One death was reported in C302 due to accidental intravenous overdose of fentanyl and alprazolam and was evaluated as not related to the study drug. The clinical reviewer agreed with the conclusion.

Drospirenone is a progestin with anti-mineralocorticoid activity, with potential for increased risk for hyperkalemia in high-risk women such as those with renal impairment, hepatic impairment, and adrenal insufficiency. The Applicant proposes a contraindication for renal impairment due to increased risk of hyperkalemia with DRSP/E4, even though most females who developed hyperkalemia in the clinical development program had only mild and or isolated increases that returned to normal while still on study medication. In the two phase 3 studies, eight subjects had hyperkalemia and two subjects discontinued due to hyperkalemia. Considering the current product contains the same dose of DRSP as Yaz®, which has a contraindication for patients with renal impairment due to a potential to develop hyperkalemia, the review team agrees with the Applicant to contraindicate the use of DRSP/E4 in women with renal impairment.

5.1 **Serious Adverse Reaction**

5.1.1 Thromboembolic Events
Two cases of venous thrombotic events were reported for DRSP/E4.

In Study C301, a 32year old white female, baseline BMI 21.4 kg/m², with no predisposition and no genetic mutations for thrombosis was found to have venous thrombosis of vena fibularis via positive D-dimer and doppler ultrasound examination during the fourth cycle of DRSP/E4 3/15 mg. The subject complained about calf pain during a study visit (study day 87) and was subsequently referred for follow-up. The study drug was discontinued. The subject was treated with rivaroxaban and changed to levonorgestrel (LNG) intrauterine system for contraception. The investigator considered the event resolved. The clinical reviewer concurred that this event is related to study drug.

In Study MIT-Es0001-C106 (C106), a 54 year old postmenopausal Caucasian women, baseline BMI 24.3 kg/m², was diagnosed with DVT three days after treatment completion of study drug. She received DRSP/E4 for total of 20 days (3/15 mg for 10 days, followed by 15/75 mg for another 10 days). The subject experienced pain and mild swelling of her right lower leg and behind her right knee after prolong car ride from the clinic site. The subject reported these symptoms in a follow-up call to the clinic the next day and was instructed to the nearest Emergency Department for evaluation of possible DVT which was confirmed by ultrasound. The subject was prescribed apixaban. Genetic testing for coagulopathy was negative. The clinical reviewer agreed with the Applicant that the adverse event of DVT is likely related to the study drug.

6 **Expected Postmarket Use**

The most likely prescribers are obstetricians and gynecologists (OB/GYN) and family or general practitioners. Nextstellis is intended for outpatient use and will likely be dispensed by outpatient pharmacies including retail pharmacies. VTE is a known risk for CHC products and providers should have an understanding of this risk when prescribing Nextstellis and other CHCs.
7  Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Nexstellis beyond routine labeling and pharmacovigilance.

8  Discussion of Need for a REMS

The clinical reviewer recommends approval of Nexstellis based on the efficacy and safety information currently available. The most commonly reported adverse events were headache, menstrual irregularities, acne, nausea, weight increased, breast pain, and abdominal pain.

Nexstellis is expected to be prescribed predominantly by OB/GYN and primary care providers. These prescribers should be familiar with associated risks of VTEs and CHCs. As with other CHC products, mitigation strategies for VTEs include a Boxed Warning, Warnings and Precaution statements, and a contraindication in labeling for women over 35 years old who smoke.

As noted in the US phase 3 study (C302), subjects with BMI > 35 kg/m$^2$ were not evaluated and there was a trend for less effectiveness with increasing BMI > 30 kg/m$^2$. The uncertainty of efficacy and safety in this population is reflected in labeling (Section 1: Indications and Usage) with a limitation of use statement to inform prescribers that Nexstellis has not been adequately evaluated in females with a BMI of >30 kg/m$^2$.

The clinical reviewer noted, although the safety database for DSRP/E4 includes more than 30,000 cycles of exposure, the maximum of 13 cycles of exposure per individual limits the ability to assess the long-term safety of these products, therefore, given Nexstellis is a new CHC product, a PMR will be required comparing the risk for fatal and non-fatal VTE and arterial thromboembolism (ATE) in new users of Nexstellis to new users of comparable CHCs in US women of reproductive age. In addition, the clinical reviewer indicated that the PMR study should be sufficiently powered for a stratified analysis by BMI to allow an assessment of the risk in obese women.

Based on currently available data and the prescribing community’s familiarity with the increased risk of VTE associated with other CHCs, Nexstellis does not pose unique safety considerations when compared to other CHCs. This reviewer is not recommending risk mitigation measures beyond professional labeling for Nexstellis.

9  Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits outweigh the risks for Nexstellis. The safety concern of increased VTE associated with Nexstellis use has been well documented in previously approved CHCs, and in general, healthcare providers who prescribe these medications should be familiar with the increase risk of VTE.

Should DUOG have any concerns or questions or if new safety information becomes available, please send a consult to DRM.
10 Appendices

10.1 REFERENCES

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

THERESA N NG
03/22/2021 12:41:47 PM

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