Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Joint Meeting of the Nonprescription Drugs Advisory Committee and the Obstetrics, Reproductive and Urologic Advisory Committee May 9-10, 2023

Location: Please note that due to the impact of this COVID-19 pandemic, all meeting participants will be joining this advisory committee meeting via an online teleconferencing platform

Topic: The committees discussed supplemental new drug application 017031/S-041, for OPILL (norgestrel) Tablet, 0.075 mg, submitted by Laboratoire HRA Pharma. OPILL is proposed for nonprescription use as a once daily oral contraceptive to prevent pregnancy.

These summary minutes for the May 9-10, 2023 joint meeting of the Nonprescription Drugs Advisory Committee (NDAC) and the Obstetrics, Reproductive and Urologic Advisory Committee (ORUDAC) of the Food and Drug Administration were approved on July 13, 2023.

I certify that I attended the May 9-10, 2023 joint meeting of the NDAC and the ORUDAC of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Moon Hee V. Choi, PharmD	Maria C. Coyle, PharmD, FCCP, BCPS, BCACP, CLS
Designated Federal Officer, NDAC	Chairperson, NDAC

Final Summary Minutes of the Joint Meeting of the Nonprescription Drugs Advisory Committee and the Obstetrics, Reproductive and Urologic Committee May 9-10, 2023

The Nonprescription Drugs Advisory Committee (NDAC) and the Obstetrics, Reproductive and Urologic Advisory Committee (ORUDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met jointly on May 9-10, 2023. The meeting presentations were heard, viewed, captioned, and recorded through an online teleconferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Laboratoire HRA Pharma. The meeting was called to order by Maria C. Coyle PharmD, FCCP, BCPS, BCACP, CLS (Chairperson). The conflict of interest statement was read into the record by Moon Hee V. Choi, PharmD (Designated Federal Officer). There were approximately 441 people online on May 9, 2023 and 426 people online on May 10, 2023. There was a total of 37 Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda:
The committees discussed supplemental new drug application (sNDA) 017031/S-041, for OPILL (norgestrel) Tablet, 0.075 mg, submitted by Laboratoire HRA Pharma. OPILL is proposed for nonprescription use as a once daily oral contraceptive to prevent pregnancy.

Attendance:

Nonprescription Drugs Advisory Committee Members Present (Voting): Elma D. Baron, MD; Maria C. Coyle, PharmD, FCCP, BCPS, BCACP, CLS *(Chairperson)*; Paul Pisarik, MD, MPH, FAAFP; Katalin E. Roth, JD, MD; Leslie Walker-Harding, MD, FAAP, FSAHM

Nonprescription Drugs Advisory Committee Members Not Present (Voting): Stephen C. Clement, MD; Diane B. Ginsburg, PhD, MS, RPh, FASHP; Tonya S. King, PhD; Ruth M. Parker, MD, MACP

Nonprescription Drugs Advisory Committee Member (Non-Voting): Mark E. Dato, MD, PhD (*Industry Representative*)

Obstetrics, Reproductive and Urologic Advisory Committee Members Present (Voting): Margery Gass, MD; Pamela A. Shaw, PhD

Obstetrics, Reproductive and Urologic Advisory Committee Member Not Present (Voting): Joseph P. Alukal, MD; Jennifer T. Anger, MD, MPH; Julia S. Barthold, MD; Esther Eisenberg, MD, MPH; Tianjing Li, MD, MHS, PhD; Michael K. Lindsay, MD, MPH; Mary B. Munn, MD; Gloria Richard-Davis, MD, MBA, NCMP, FACOG; Kristine E. Shields, MSN, DrPH (*Consumer Representative*)

Obstetrics, Reproductive and Urologic Advisory Committee Member Present (Non-Voting): Michelle C. Fox, MD, MPH, FACOG (*Industry Representative*)

Temporary Members (Voting): Deborah K. Armstrong, MD; Cynthia Baur, PhD; Abbey Berenson, MD, PhD; Elise D. Berlan, MD, MPH, FAAP; Jesse Catlin, PhD; Kathryn Curtis, PhD; Eve Espey, MD, MPH; Sabrina Everhart (*Patient Representative*); Jolie Haun, PhD, EdS; Suzanne B. Robotti (*Acting Consumer Representative*)

FDA Participants (Non-Voting): Peter Stein, MD; Karen Minerve Murry, MD; Pamela Horn, MD; Christine P. Nguyen, MD; Audrey Gassman, MD; Barbara Cohen, MPA; Jeena Jacob, MD, PharmD; Anandi Kotak, MD, MPH

Designated Federal Officer (Non-Voting): Moon Hee V. Choi, PharmD

Open Public Hearing Speakers Present: Kristyn Brandi, MD, MPH, FACOG (American College of Obstetricians and Gynecologists); Sophia Phillips (National Center for Health Research); Don Downing, RPh; David C. Spangler (Consumer Healthcare Products Association); Shelby Davies (North American Society for Pediatric and Adolescent Gynecology); Lisa B. Haddad, MD, MPH; Miriam Yeung; Rebecca "Bex" Heimbrock; Jamie L. Manson, M.Div. (Catholics for Choice); Caroline Renko (PharmedOut); Kelly Blanchard (Ibis Reproductive Health); Angela Maske (Advocates for Youth); Daniel Grossman, MD; Brianna Nelson; Sriha P. Srinivasan; Krishna Upadhya, MD, MPH (Planned Parenthood Federation of America); Robin Watkins, CNM, WHNP-BC (Health Care at Power to Decide); Susan Muskett (Pro-Family Women); Lin-Fan Wang, MD, MPH; Jacquiline Blanco, BSN, RNC; Jamila Perritt, MD, MPH, FACOG (Physicians for Reproductive Health); Miyana Evans (Black Women for Wellness); Nicole Martin (Indigenous Women Rising); Monifa Bandele, MHS (MomsRising); Megan L. Kavanaugh, DrPH (Guttmacher Institute); Komkwuan Paruchabutr, DNP, FNP-BC, WHNP-BC, CNM, FACNM (The National Association of Nurse Practitioners in Women's Health); Dyvia Huitron; Charlene Bencomo (Bold Futures NM); Clare Coleman (National Family Planning & Reproductive Health Association); Leng Leng Chancey (9to5, National Association of Working Women); Atsuko Koyama, MD, MPH (Doctors for America); Candace Gibson (National Latina Institute for Reproductive Justice); Cherie Priya Dhar, MD (Society for Adolescent Health and Medicine); Victoria Nichols (Free the Pill Coalition); Sally Rafie, PharmD, BCPS, APh, NCMP, FCCP, FCPhA (Birth Control Pharmacist); Lauren Schenk; Pratima Gupta, MD, MPH

The agenda was as follows:

Day 1: May 9, 2023

Call to Order and Introduction of Committee	**Maria C. Coyle, PharmD, FCCP, BCPS, BCACP, CLS** Chairperson, NDAC
Conflict of Interest Statement	**Moon Hee V. Choi, PharmD** Designated Federal Officer, NDAC
FDA Opening Remarks	**Pamela Horn, MD** Director Division of Nonprescription Drugs II (DNPD II) Office of Nonprescription Drugs (ONPD) Office of New Drugs (OND), CDER, FDA

APPLICANT PRESENTATIONS	**Laboratoire HRA Pharma**
Introduction	**Helene Guillard, PharmD** Global Rx-To-OTC Switch Director Women's Health HRA Pharma / Perrigo
Need for Nonprescription Oral Contraception	**Carolyn Westhoff, MD, MSc** Sarah Billinghurst Solomon Professor of Reproductive Health Department of Obstetrics and Gynecology Professor of Population and Family Health and Epidemiology Mailman School of Public Health Columbia University
Consumer Behavior Studies and ACCESS Study Design Self-Selection Results	**Russell Bradford, MD, MSPH** Senior Vice President, Medical Affairs PEGUS Research
Clinical Interpretation of Potential Risk of POP Use in Breast Cancer Survivors	**Pamela Goodwin, MD, MSc, FRCPC, FASCO** Senior Scientist Lunenfeld-Tanenbaum Research Institute Sinai Health System Professor of Medicine University of Toronto
ACCESS Actual Use Adherence Results	**Irene Laurora, PharmD** Senior Director, Scientific Affairs Women's Health, HRA Pharma / Perrigo
Expert Interpretation of ACCESS Adherence Results	**Arthur Stone, PhD** Professor of Psychology, Economics, and Public Policy Director Dornsife Center for Self-Report Science University of Southern California Emeritus Distinguished Professor of Psychiatry & Behavioral Science Stony Brook University School of Medicine
ACCESS Actual Use Adherence Conclusions	**Irene Laurora, PharmD**

APPLICANT PRESENTATIONS (CONT.)

Clinical Interpretation of ACCESS Results and Considerations Around Effectiveness	**Stephanie Sober, MD, MSHP** Global Lead Medical Affairs Women's Health, HRA Pharma / Perrigo
Clinical Perspective	**Anna Glasier, MD, Dsc, OBE** Professor at Edinburgh and London Universities
Clarifying Questions	

LUNCH

FDA PRESENTATIONS

Introduction	**Pamela Horn, MD**
Efficacy and Safety of Prescription Norgestrel Tablet and Implications for the Nonprescription Setting	**Anandi Kotak, MD, MPH** Medical Officer Division of Urology, Obstetrics, and Gynecology Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine, OND, CDER, FDA
Consumer Behavior Studies (Label Comprehension, Targeted Breast Cancer Self-Selection and Self-Selection in ACCESS)	**Barbara Cohen, MPA** Social Science Analyst DNPD II, ONPD, OND, CDER, FDA
ACCESS Study Use Phase: Design and Conduct	**Jeena Jacob, MD, PharmD** Medical Officer DNPD II, ONPD, OND, CDER, FDA
ACCESS Study Use Phase: Use and Adherence Endpoints	**Rongmei Zhang, PhD** Mathematical Statistician Division of Biometrics VII Office of Biostatistics Office of Translational Sciences, CDER, FDA
ACCESS Study Use Phase: Secondary Endpoints and Safety Findings from Uncontrolled and Postmarketing Data	**Jeena Jacob, MD, PharmD**
Summary	**Pamela Horn, MD**
Clarifying Questions	

BREAK

OPEN PUBLIC HEARING

ADJOURNMENT

Day 2: May 10, 2023

Call to Order and Introduction of Committee	**Maria C. Coyle, PharmD, FCCP, BCPS, BCACP, CLS**
Conflict of Interest Statement	**Moon Hee V. Choi, PharmD**
Charge to the Committee	**Pamela Horn, MD**
Questions to the Committee/Committee Discussion	

LUNCH

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committees:

1. **DISCUSSION**: Discuss whether consumers are likely to use norgestrel tablet in a safe and effective manner, considering the possibility of unintended pregnancy with incorrect use.

   Specifically, discuss whether consumers are likely to adhere to taking the tablet daily at the same time of day, based solely upon the nonprescription labeling without any assistance from a healthcare professional.

   Please discuss for the following consumer populations:

   a. General population of females of reproductive potential
   b. Adolescents
   c. Those with limited literacy
   d. Those using concomitant products (e.g., anticonvulsant drugs) that may interact with and reduce efficacy of norgestrel tablet

   Committee Discussion*: The committee members agreed that the general population of females of reproductive potential are likely to use norgestrel tablet in a safe and effective manner in the over-the-counter (OTC) setting, primarily based on broad clinical experience as well as the data presented. In regard to the challenges with adherence and the possibility of unintended pregnancies with incorrect use, these committee members expressed that consumers are likely to use norgestrel in a safe and effective manner without assistance from a healthcare provider. Many committee members agreed adolescents are likely to use norgestrel tablet in a safe and effective manner and noted the following: 1) adolescents are healthier compared to other women*

of reproductive ability 2) adolescents are at the highest risk of unintended pregnancy 3) absolute risk of harm from inappropriate use is low in the population and 4) lack of access is the greatest barrier. One committee member stated that they were concerned that adolescents and older consumers would not understand the instructions for use and that this could result in less effective use. The general discussion between the committee members involving consumers with limited literacy agreed that this group is at the highest risk for unintended pregnancy and thus, would make these consumers a priority group to benefit from availability in a nonprescription setting, adding that for this group, the main barrier is also lack of access. The committee members did not comment on the limitations of the data in the application to inform likelihood of safe and effective use in consumers, including those with limited literacy. Lastly, the committee members did not express concern with norgestrel use in a safe and effective manner in consumers that are using concomitant products that may interact with and reduce efficacy of norgestrel tablet. These committee members stated that: 1) consumers using concomitant products would more than likely be in the care of a provider 2) generally, very few medications have been shown to lower the effectiveness of contraceptives and 3) there is no major concern for those individuals using multiple hormonal contraceptives simultaneously as it is not uncommon to prescribe two hormonal contraceptives at one time. Please see the transcript for details of the Committees' discussion.

2. **DISCUSSION**: The ACCESS Study- Use Phase had improbable dosing in approximately 1/3 of participants. If FDA were to recommend the Applicant conduct another Actual Use Study (AUS), what changes to the AUS design would the committee recommend? Consider the following:

    a. e-diary design
    b. e-diary recall period
    c. Participant compensation structure
    d. Methods ensuring e-diary data entry instructions are adequately comprehended
    e. Incorporating a pathway allowing participants to ask a healthcare provider (HCP) before deciding study drug purchase
    f. Study questions to determine timing of when participants spoke to an HCP during the study

    ***Committee Discussion**: The committee members stressed the importance of not delaying the availability of norgestrel tablets in the nonprescription setting. However, if FDA were to recommend the Applicant conduct another AUS, the following changes to the study design were recommended: 1) resources available for participants to seek support with the e-diary platform or product itself 2) a study to include daily reminders requiring data entry at the time of dose and thus alleviating the issues around missing data or over-reporting 3) qualitative inquiry from study staff/nurse interviewers 4) reevaluating how best to compensate participants in a manner that is not based on the number of direct entries and 5) an opportunity for "teach back" mechanism to confirm participants understood the e-diary data instructions. Some members recommended piloting the e-diary to ensure usability before the study conduct. Please see the transcript for details of the Committees' discussion.*

3. **DISCUSSION**: Discuss whether there is sufficient information to conclude consumers in the following scenarios will appropriately deselect from norgestrel use:

    a. Consumers with a history of or current diagnosis of breast cancer

b. Consumers with abnormal vaginal bleeding of undiagnosed etiology
c. Consumers who are using other hormonal contraceptives

***Committee Discussion**: The committee members agreed that there is sufficient information to conclude consumers with a history of or current diagnosis of breast cancer would not select to use norgestrel. One committee member noted that anyone with a history of breast cancer would almost always be under the care of an oncologist and would be cognizant to avoid hormonal drugs and that even in women with hormone-receptor-negative breast cancer, this product would be something that an oncologist would stress to avoid.*

In regard to the potential for norgestrel use in consumers with abnormal vaginal bleeding, one committee member stated that one of the most frequent reasons for seeing a women's healthcare provider is abnormal bleeding, and thus, this committee member did not have concerns that serious causes of abnormal vaginal bleeding would be missed. Another committee member agreed by noting that 72% of participants from the study did report to a healthcare professional for unexplained vaginal bleeding and the committee found that reassuring.

The committee members did not have concerns that consumers who are using other hormonal contraceptives would appropriately select not to use norgestrel. Please see the transcript for details of the Committees' discussion.

4. **VOTE**: Is there adequate information to conclude that consumers will be likely to use norgestrel tablet properly, such that the benefits of making this available for nonprescription use (access without needing to interact with a healthcare professional), exceed the risks (such as inadequate adherence leading to contraceptive failure with unintended pregnancy, use of the medication by consumers with a contraindication to its use, failure to see a health care professional when appropriate)?

    a. If you voted 'No', explain why you believe the risks outweigh the benefits for nonprescription use, and what additional data would be necessary to support approval.

    b. If you voted 'Yes', explain why you believe the benefits outweigh the risks for nonprescription use.

Vote Result: Yes: 17 No: 0 Abstain: 0

***Committee Discussion**: The committee members unanimously agreed that there was adequate information to conclude that the majority of consumers will be likely to use norgestrel tablet properly, such that the benefits of making this available for nonprescription use exceed the risks. Committee members agreed that there were some concerns on the data in adolescents and limited literacy populations, but that the rare and unlikely harms are outweighed by the overall benefits of improved access without the current barriers and restrictions, and opined that nonprescription availability will have a tremendous positive impact to women and public health. Please see the transcript for details of the Committees' discussion.*

The meeting was adjourned at approximately 1:47 p.m. ET.