FDA Briefing Document

Joint Meeting of the Nonprescription Drugs Advisory Committee and the Obstetrics, Reproductive, and Urologic Drugs Advisory Committee
May 9, 2023 – May 10, 2023

NDA 017031, Supplement 41

Drug name: norgestrel tablet, 0.075 mg

Applicant's proposed proprietary name for product: Opill

Applicant: Laboratoire HRA Pharma

Division of Nonprescription Drugs 2 / Office of Nonprescription Drugs

Division of Urology, Obstetrics, and Gynecology / Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine

Division of Biometrics 7 / Office of Biostatistics

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Glossary

AADPBU	ask a doctor or pharmacist before use
ACCESS	Adherence with Continuous-Dose Oral Contraceptive: Evaluation of Self-Selection and Use
AC	Advisory Committee
AE	adverse event
AUS	actual use study
BD	briefing document
BMD	bone mineral density
CI	confidence interval
CIL	consumer information leaflet
CDC	Center for Disease Control and Prevention
DFL	Drug Facts label
EOS	end-of-study
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
HCP	healthcare provider
IA	integrated assessment
IND	Investigational New Drug
IR	information request
IUD	intrauterine device
LB	lower bound of the confidence interval
LCS	label comprehension study
LNG	levonorgestrel
NAAL	National Assessment of Adult Literacy
NDA	new drug application
PD	pharmacodynamic
PDP	principal display panel
PI	Pearl Index
PK	pharmacokinetic
POP	progestin-only oral contraceptive pill
REALM	Rapid Estimate of Adult Literacy in Medicine
SAE	serious adverse event
SS	self-selection
SSP	self-selection phase
UP	use phase

USPI	United States Prescribing Information
TBCSS	targeted breast cancer self-selection study

1 Executive Summary and Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the Advisory Committee Meeting

The FDA is convening this Advisory Committee (AC) meeting to discuss the proposed first-in-class prescription-to-nonprescription switch of norgestrel tablet 0.075 mg (norgestrel tablet), a progestin-only oral contraceptive pill (POP), for the prevention of pregnancy in females of reproductive potential. Of particular importance is discussion of the submitted data pertaining to:

- How likely consumers are to use the product in an effective and safe manner, using only the nonprescription labeling and without any assistance from a healthcare professional, and
- Whether consumers who should not use the product will not use it (i.e., whether consumers will appropriately self-"deselect")

1.2 Context for Issues to be Discussed at the Advisory Committee

In the United States, approximately 3 million unintended pregnancies occur each year (Finer and Zolna 2016). Unintended pregnancy is associated with negative maternal, fetal, and perinatal outcomes (Dibaba et al. 2013; Lindberg et al. 2015). The risks of unintended pregnancy can be reduced with effective use of contraception.

Currently, contraceptive methods available without a prescription include male condoms, spermicides, and female condoms, and are used on an as-needed basis. These methods are associated with a >10% failure rate during the first year of typical use and are less effective than prescription methods available through interaction with a healthcare provider (HCP) (Trussell et al. 2018). Available contraceptive methods requiring interaction with a HCP consist of reversible contraceptives and permanent sterilization. Prescription contraceptive methods include oral contraceptives (combined estrogen and progestin, or progestin-only), contraceptive patches, vaginal rings, injectable hormonal contraceptives, hormonal implants, and intrauterine devices (IUDs). Permanent sterilization includes tubal ligation and vasectomy. Oral contraceptives are the most commonly used reversible method of contraception. Oral contraceptives are recommended to be taken daily at approximately the same time; adherence to daily use at the same time of day is essential for the effectiveness of POPs.

The availability of a nonprescription daily oral contraceptive is expected to reduce barriers that females of reproductive potential experience in obtaining effective methods of contraception. If data support nonprescription approval, this progestin-only daily oral contraceptive (norgestrel tablet) could provide an alternative contraceptive choice to consumers that, if used correctly, would be more effective than the currently available nonhormonal, use-as-needed contraceptive choices that are available without a prescription (Trussell et al. 2018). The safety and effectiveness of norgestrel tablet in a nonprescription setting, however, is contingent on whether a consumer can appropriately self-select and adhere closely to the directions for use, or correctly choose not to use the product (deselect).

The ability of consumers to appropriately deselect is vital because this product has important risks that are different from the risks associated with currently available nonprescription contraceptive methods, including risks associated with a history of breast cancer or other progestin-sensitive cancers, vaginal bleeding of undiagnosed etiology, and use of medications that may interact with norgestrel (drug-drug interactions). Norgestrel use in consumers with a history of breast cancer and other progestin-sensitive cancers may stimulate growth of progesterone-receptor positive tumor cells and can increase the risk of recurrence in breast cancer survivors with a history of progesterone-receptor positive tumors. Abnormal uterine bleeding can be a sign of a medical condition such as malignancy, ectopic pregnancy, thyroid

disorders, or bleeding diathesis that requires medical evaluation and treatment. Using medications that interact with norgestrel can result in decreased efficacy of norgestrel or the other medication or both. The consequences of this can be severe, potentially resulting in unintended pregnancy or seizures in an individual with a seizure disorder. Therefore, FDA emphasizes deselection as the critical endpoint in self-selection studies.

1.3 Brief Description of Issues for Discussion at the AC

On June 14, 2022, the Applicant submitted a supplemental NDA to support a prescription-to-nonprescription switch of norgestrel tablet with a proposed use "to prevent pregnancy" in females of reproductive potential. For approval of a product for use in the nonprescription setting, FDA requires that the Applicant demonstrate that the product can be used by consumers safely and effectively relying only on the nonprescription drug labeling without any assistance from a healthcare professional. The Applicant's studies to support this application discussed in this briefing document include:

- **Label comprehension study (LCS) of the Drug Facts label (DFL) and the Targeted Breast Cancer Self-Selection study (TBCSS):** a combined LCS of the DFL and targeted breast cancer self-selection study. This combined study consisted of a noninterventional assessment of understanding of the DFL among consumers with and without breast cancer, and of deselection for use of the product in consumers with breast cancer.
- **LCS of the Consumer Information Leaflet (CIL)**: a noninterventional assessment of understanding of the CIL, a document with additional consumer information that accompanies the DFL in the product packaging
- **Adherence with Continuous-Dose Oral Contraceptive Evaluation of Self-Selection and Actual Use (ACCESS) study:** this actual use study (AUS) consisted of two phases: a noninterventional assessment of self-selection (ACCESS Self-Selection Phase(ACCESS-SSP)) followed by an interventional assessment of self-reported actual use and safety (ACCESS Use Phase (ACCESS-UP))
- **Delayed tablet intake study (Study 002)**: an interventional study assessing pharmacodynamic (PD) parameters of norgestrel tablet for daily use.

The Applicant also submitted postmarketing safety data, literature reviews, and analyses of specific safety topics relevant to use of norgestrel tablet as a daily oral contraceptive.

The first three specific studies described above are referred to as consumer behavior studies. In most nonprescription drug development programs, consumer behavior studies are the key evidence to support conclusions about whether consumers are likely to be able to use a drug safely and effectively in the nonprescription setting, using only the drug's labeling, and without input from healthcare professionals. Consumer behavior studies usually have multiple endpoints, with some designated as critical due to their clinical importance, and other endpoints designated as less critical. Established target thresholds (lower bound of the 90% confidence interval (CI)) for the critical endpoints in consumer behavior studies are typically set at 90%, reflecting their clinical importance.

Assessment of consumers' ability to correctly use norgestrel tablet, and therefore achieve effective use, included the following key endpoints:

- Adherence to daily dosing instructions (primary endpoints in the ACCESS-UP)
- Comprehension of important Directions for Use (e.g., importance of taking a tablet daily and at the same time every day; what to do in the event of a delayed or missed tablet, and how to switch from taking another contraceptive) (primary endpoints in LCS-DFL and LCS-CIL)

Assessment of the safe use of norgestrel tablet in the nonprescription setting included evaluation of:

- Ability to comprehend and appropriately deselect from norgestrel tablet use in individuals with a "Do not use" condition (i.e., breast cancer, concomitant use with other hormonal contraception) (primary endpoints in DFL LCS; primary endpoint in Targeted Breast Cancer Self-Selection Study; primary endpoint in ACCESS-SSP).
- Ability of individuals with a history or current diagnosis of breast cancer to deselect appropriately from norgestrel tablet use (primary endpoint in Targeted Breast Cancer Self-Selection Study; primary endpoint in ACCESS-SSP).
- Ability to comprehend key safety messages such as when to seek medical attention while using norgestrel tablet (primary endpoints in LCS-DFL).

Based on these data, FDA has identified the following key issues for the advisory committee to consider:

1. **Adequacy of evidence of correct use/adherence**: In the ACCESS study, FDA found that a substantial portion of individuals overreported the number of tablets they took (reported taking more tablets than dispensed). The improbable dosing and the substantial proportion of subjects with improbable dosing, without identifiable root cause(s), call into question the reliability of all of the actual use data in ACCESS-UP—therefore not providing reliable information to assess an individual's ability to appropriately use this product.

We ask the AC to consider whether the improbable dosing (and extent of this) undermines the reliability of the study, and results in inadequate information to determine whether consumers can appropriately use norgestrel.

2. **Comprehension and deselection in females with a history of or current breast cancer**: Hormonal contraception (including POPs), is contraindicated (meaning that the benefits are considered never to outweigh the risks) in females with a history of, or current, breast cancer. Comprehension of this contraindication did not approach the prespecified target threshold in the LCS, and there were participants who failed to correctly deselect in the targeted breast cancer and ACCESS self-selection studies.

We ask the AC to consider whether females with a history of or current diagnosis of breast cancer will adequately comprehend and appropriately deselect from using norgestrel tablet in a nonprescription setting.

3. **Comprehension and deselection in females with abnormal vaginal bleeding of undiagnosed etiology**: Abnormal vaginal bleeding could indicate a hormonally sensitive condition (e.g., uterine cancer) that needs to be evaluated and diagnosed prior to using hormonal contraceptives, including POPs. Relevant findings from the norgestrel tablet consumer studies follow:
    - Comprehension of the warning "Ask a doctor before use if you currently have vaginal bleeding between your periods and you have not already talked to your doctor" scored below the prespecified target threshold for comprehension in the DFL LCS.
    - In the ACCESS-SSP, more than half of the participants who stated in the enrollment interview that they had unexplained vaginal bleeding and had not discussed it with their doctor incorrectly indicated norgestrel would be appropriate for them to use.
    - In the ACCESS-UP, close to a quarter of participants who reported unexplained vaginal bleeding between menstrual periods prior to initiating use of norgestrel reported that they neither spoke to a HCP about unexplained vaginal bleeding before use of the study drug nor at any time during the study.

We ask the AC to consider whether females with undiagnosed abnormal vaginal bleeding will comprehend and appropriately deselect from using norgestrel tablet in a nonprescription setting.

4. **Concomitant use of norgestrel tablet with other hormonal contraceptives**: The proposed DFL warns the consumer "Do not use together with another birth control pill, vaginal ring, patch, implant, injection or an IUD (intra-uterine device)." In the DFL LCS, comprehension of this statement met the prespecified target threshold. However, 11 participants (1%) reported using a hormone-containing birth control product while using norgestrel in ACCESS. Of these 11 participants, 8 were using a hormone-containing birth control product at enrollment, and the remaining 3 initiated use of another hormone-containing birth control product or IUD after enrolling in the study, despite the "Do not use" warning on the proposed DFL.

We ask the AC to consider whether consumers will understand and avoid using concomitant hormonal contraceptives with norgestrel in a nonprescription setting.

5. **Adolescent understanding of correct use of norgestrel tablet**: Lack of information regarding sexual history and sexual activity, and small sample size, limit the assessment of appropriate norgestrel tablet use in adolescents. Because information regarding sexual history and sexual activity was not obtained, FDA was unable to assess whether adolescents in ACCESS were at risk for pregnancy or performed correct mitigating behaviors, such as use of additional nonhormonal contraception, when indicated (e.g., after missed doses). Younger adolescents are under-represented (49 participants age <15 years, 3 participants aged 12 years, and no participants aged ≤11 years) in the study population. Younger adolescents (11 to 14 years old) demonstrated low comprehension of important labeling messages regarding: a) the need for additional nonhormonal contraception (e.g., condoms) when first starting the drug or after missing a dose; and b) starting the next pack the day after finishing the last one. Moreover, this age group also scored low in comprehension of "Do not use as an emergency contraceptive."

We ask the AC to consider whether adolescents will correctly use norgestrel tablet in a nonprescription setting.

6. **Comprehension, appropriate deselection, and correct use in individuals with limited literacy:** FDA typically asks applicants to include approximately one-third limited literacy representation in their consumer studies to reflect population-based estimates. The DFL and CIL LCSs had 26% and 25% limited literacy participation, respectively. While targeted self-selection studies may have a somewhat lower limited literacy representation due to difficulties in recruiting for certain medical conditions, the targeted breast cancer self-selection study had only 5% limited literacy participation. Only 13% of participants in the self-selection population of ACCESS had limited literacy and 14% of participants in the User Population of the ACCESS study had limited literacy. Overall, the proportion of participants with limited literacy may not be reflective of the anticipated consumer population for this product.

We ask the AC to consider whether consumers with limited literacy will correctly use norgestrel tablet in a nonprescription setting.

1.4 Draft Points for Consideration

The Applicant seeks approval of norgestrel tablet to prevent pregnancy in females of reproductive potential of all ages in the nonprescription setting. We request the AC to consider the following questions:

1. Based upon available information, discuss whether consumers are likely to use norgestrel tablet in a safe and effective manner, and the implications for efficacy. Specifically, discuss whether consumers are likely to adhere to taking the tablet daily at the same time of day, based upon the

nonprescription labeling without any assistance from a healthcare professional. Please discuss for the following consumer populations:

   a. The general population of females of reproductive potential
   b. The adolescent population
   c. The limited literacy population

2. The ACCESS-UP had improbable dosing results for approximately 1/3 of participants. If FDA were to recommend the Applicant conduct another 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 to ensure study instructions regarding e-diary data entry are adequately comprehended by participants
   e. Incorporating a pathway that allows participants to ask their doctor before deciding whether to purchase the study drug
   f. Study questions to determine the timing of when participants spoke to a HCP during the study
3. Discuss whether there is sufficient information to conclude that consumers in the following scenarios will appropriately deselect from use of this product:
   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.
4. VOTE: Is there adequate information to conclude that consumers will be likely to properly use norgestrel tablet such that the benefits of making this available for nonprescription use (access without needing to interact with a healthcare professional), exceed the risks (contraceptive failure due to inadequate adherence, using this medication when they have 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.

We look forward to a thorough and reasoned discussion of these complex, important matters. Thank you in advance for the vital public health contribution you are making through your participation in this meeting.

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

The Centers for Disease Control and Prevention (CDC) defines an unintended pregnancy as either unwanted, occurring when no children or no more children were planned, or mistimed, occurring earlier than planned. Almost half of the 6.1 million pregnancies in the United States each year are unintended (Finer and Zolna 2016). Among 15-to-17 year-olds in the United States, 72% of pregnancies were unintended. While national data on the proportion of pregnancies in adolescents 14 years or younger are not available, it is likely unintended pregnancies represent an even larger percent of total pregnancies in this age group (Kost et al. 2013). Analysis of results from national surveys and national data show unintended pregnancies disproportionally impact lower income women, those aged 20 to24

years, black women, and those who have not completed high school (Finer and Zolna 2016). Unintended pregnancies have been linked to negative maternal and perinatal outcomes, including reduced likelihood of receiving early prenatal care (Dibaba et al. 2013; Lindberg et al. 2015) and increased risk of preterm delivery, with attendant adverse neonatal, developmental, and child health outcomes (Mohllajee et al. 2007; Shah et al. 2011).

Currently available contraceptive nonprescription products in the United States include male condoms, spermicides, and female condoms. They are used at the time of sexual activity (on an as-needed basis) and are associated with a >10% failure rate during the first year of typical use. Prescription contraceptive products available through interaction with a HCP, such as daily oral contraceptives, contraceptive patches, vaginal rings, and injectable hormonal contraceptives, are to be used regardless of sexual activity and are user-dependent. These products are associated with >1%-10% failure rate during the first year of typical use. Contraceptive methods with a ≤1% failure rate during the first year of typical use, such as hormonal implants, IUDs, tubal ligation, and vasectomy, are available in the United States through interaction with a HCP and are not user-dependent (Trussell et al. 2018). Among the prescription reversible contraceptive products (tubal ligation and vasectomy are considered irreversible), oral hormonal contraceptives, which include those that include an estrogen plus a progestin (combined hormonal contraception; may be oral or non-oral) and those containing only a progestin (POP), are the most commonly used. For efficacy, both combined oral contraceptives and POPs require taking a tablet at approximately the same time each day; however, most POPs are more susceptible to contraceptive failure with delayed or missed tablets, whereas such precise timing is more flexible with combined oral contraceptives. Because of the more stringent timing needed with POPs for contraceptive efficacy, the use of POPs in clinical practice are generally reserved for those who cannot or prefer not to use estrogen-containing contraception, such as lactating females.

The advantages of the availability of a nonprescription oral hormonal contraceptive include reducing potential barriers females of reproductive potential experience in obtaining effective methods of contraception. The safety and efficacy of norgestrel tablet for pregnancy prevention in the prescription setting has been established with the approval of the original NDA in 1973. As a potential nonprescription contraceptive, this POP can provide consumers with an oral contraceptive choice that has lower typical use failure rates than other nonprescription contraceptive choices currently available (Trussell et al. 2018). However, the contraceptive efficacy advantage of norgestrel tablet over currently available nonprescription options is clearly contingent on compliance and adhering closely to the directions for use, and norgestrel failure modes may not be obvious to the consumer. For example, if a condom is not used at the time of sexual activity, it is evident one is at risk for pregnancy, and the consumer may choose to use emergency contraception in a timely manner to prevent pregnancy. If POP is not used correctly (e.g., POP is taken daily but at variable timing over multiple days), the consumer may not recognize the risk of pregnancy and emergency contraception may not be used in a timely manner.

2.2 Pertinent Drug Development and Regulatory History

Prescription Drug Development and Regulatory History

FDA approved Ovrette (norgestrel) tablet, 0.075 mg in October 1973 under NDA 017031 as a prescription product for the prevention of pregnancy. Ovrette is a progestin-only oral contraceptive (it does not contain an estrogen component) and is indicated for use by females of reproductive potential. It is to be taken once daily at the same time every day, and continuously, without interruption between tablet packs. According to the approved prescription labeling, it works by “suppressing ovulation in approximately half of the cycles in users, thickening the cervical mucus to inhibit sperm penetration,

lowering the midcycle luteinizing hormone and follicle-stimulating hormone peaks, slowing the movement of the ovum through the fallopian tubes and altering the endometrium" (refer to Section 5.1). The original NDA relied on eight clinical studies that provided data on the safety and efficacy of the product.

On June 7, 2005, Ovrette was discontinued from sale in the United States due to lack of marketing and not for reasons related to safety or efficacy issues. On August 15, 2017, the Applicant updated the prescription labeling and patient package insert in consideration of reintroducing into marketing the product but as a nonprescription drug. The Applicant also proposed changing the proprietary name from Ovrette to Opill.

Nonprescription Drug Development and Regulatory History

The Applicant had multiple meetings and discussions with FDA regarding the prescription-to-nonprescription drug development program. In the first early development meeting, the Applicant's proposal included a targeted self-selection study in breast cancer patients and Self-Selection (SS) and AUS in adults and adolescents in the general population.

During subsequent interactions, FDA offered advice on various aspects of the SS/AUS protocol and Drug Facts label (DFL). Those interactions are briefly summarized below.

- Regarding the study population for the SS/AUS, FDA advised having a limited literacy representation of at least 30% for both adults and adolescents and to increase the number of adolescents to include at least 50 adolescents under 15 years and 125 adolescents between 15 to 17 years. The Applicant agreed to do its best to increase the total adolescent population as advised.
- Regarding the SS/AUS IND-opening protocol, the Multicenter Oral Contraceptive Pill Use Study Conducted In an OTC Naturalistic Environment (OPTION) study, FDA advised that the study duration be 6 months to capture adequate efficacy and safety data in the nonprescription setting. The study was terminated early, due to technical failures in the daily use of the electronic diary (e-diary) as well as other associated issues with data collection and monitoring tools that were designed for the study.
- Regarding the new, second SS/AUS protocol, the ACCESS study, FDA advised that the adolescent age range be extended down to age 11 years.
  - FDA also noted that it was important to take steps to address the issues with the e-diary collection systems that disrupted the previous SS/AUS study. FDA requested those changes to the e-diary process be submitted for better understanding of the problems with data collection. The Applicant submitted the OPTION Clinical Study Report in March 2020, which contained information regarding the e-diary failure in OPTION. In this report the issues described included users of the platform not being able to locate participants' casebooks in the system, users not being able to conduct interviews with participants they could not search by name, and certain personnel being able to view participants' personal identifiable information. These issues led the Applicant to use a different vendor for the data management system in the subsequent ACCESS study.
- Regarding the data in the young adolescent cohort for the SS/AUS, the Applicant provided the results of recruitment effort and reported that they had only recruited 12 participants under the age of 15 years as of March 2020. FDA stated that these data may not be adequate to support a marketing application. FDA stated that use in adolescents is an area of concern and could be a topic of discussion at a future AC meeting.

- FDA recommended that the Applicant perform a critical review of the literature and summarize its understanding of the effects of available progestin-only contraceptives on peak bone mass accrual in adolescents as a safety topic.
- FDA communicated areas of concern regarding key safety messages on the proposed DFL; these included revisions to the subheadings that pertained to "stop use and ask a doctor if" and "stop use and seek medical help right away" warnings to help optimize effective communication of key safety messages on the proposed DFL.
  - FDA also recommended more clearly defining the types of bleeding to enhance consumer comprehension, due to preliminary Label Comprehension Study results that appeared to indicate consumers had difficulty with the phrase "unexplained vaginal bleeding."
- FDA provided advice to revise the "Ask a doctor before use if" cancer warning from "you have or ever had any cancer" to "if you have or ever had other types of cancer" to more clearly differentiate other types of cancer from breast cancer. The Applicant did not revise this element of the proposed DFL.

3 Summary of Issues for the AC

3.1 Contraceptive Efficacy Issues

The contraceptive efficacy of norgestrel tablet was established with the original approval for prescription use in 1973. This section discusses some of the issues inherent in the assessment of contraceptive efficacy in the context of the current U.S. population that is likely to use this product.

3.1.1 Determination of Contraceptive Efficacy of Norgestrel Tablet

The contraceptive efficacy endpoint of interest (i.e., pregnancy) for contraceptive products is calculated using Pearl's formula (i.e., Pearl Index [PI]). The Pearl Index represents the proportion of females who become pregnant, out of 100, during one continuous year of using only the contraceptive product investigated (i.e., no other contraceptive methods used). The formula for calculating the PI follows:

Equation 1. Pearl Index

$$\text{Pearl Index} = \frac{(\text{Number of pregnancies}) \times 13 \text{ cycles}}{\text{Number of 28-day cycles as defined below}} \times 100$$

Calculation of the PI currently requires documentation of:

- Pregnancy with an estimated date of conception between the date of first study product use through seven days after the last study product use. This is referred to as "on-treatment pregnancy."
- And complete or incomplete on-treatment cycles in which vaginal intercourse occurred and no additional nonhormonal (i.e., "back-up" contraception such as condoms) or emergency contraception was used based on participant diary data. These cycles are referred to as "evaluable cycles."

FDA recommends the PI as the primary endpoint for all studies intended to demonstrate substantial evidence of effectiveness for prescription hormonal contraceptive products (July 2019). For the purpose of a prescription-to-nonprescription switch, the product's intrinsic efficacy as a contraceptive is considered to have been established with the initial approval of the product under the prescription setting.

3.1.2 Contraceptive Efficacy Issues in Detail

3.1.2.1 Efficacy Issue #1: Estimating Norgestrel's Pearl Index for the Nonprescription Setting

Although the contraceptive efficacy of norgestrel as a prescription product was established at the time of approval, limitations in the sources of data outlined below preclude precise estimates of the contraceptive efficacy of norgestrel tablet 0.075 mg as it is intended to be used (i.e., taken daily at approximately the same time every day).

Table 1 compares the estimated Pearl Index for norgestrel tablet 0.075 mg as a prescription product across available studies and in the ACCESS study.

Table 1. Pearl Index for Norgestrel Tablet 0.075 mg

Source	Year(s)	Pearl Index (Per 100 Women-Years)	Limitations
Original approval	1970-1973	2.3**	Includes females ages 15-49[†] Includes all cycles[‡]
Meta-analysis*	1968-1993	1.96 (range 1.18-6.87)	Based on published literature Heterogeneity of study designs, study populations, and sample sizes Inconsistent methodologies, and varying durations Several studies conducted ex-U.S. Some studies included lactating females
ACCESS Actual Use Study – Applicant analysis	2019-2021	2.2[¥]	Based on 6 on-treatment pregnancies for the entire user population
ACCESS Actual Use Study – FDA Analysis		3.4[¥]	Based on 9 on-treatment pregnancies for the entire user population 2 pregnancies in females with BMI 25 to < 30 kg/m^2 [€] 3 pregnancies in females with BMI ≥ 30 kg/m^2[€]
ACCESS Actual Use Study – FDA Analysis: Excluding Improbable Dosing		4.4[£]	Based on 8 on-treatment pregnancies[§] and AUSDs in the probable dosing cohort

Source: FDA Reviewer Analysis; NDA 017031 Action Package; NDA 017031 S-035, S-036, S-041.
* Conducted and submitted by the Applicant.
** Composite of the eight smaller efficacy studies (total study population 1,950 females). Confidence intervals were not calculated.
† Current practice is to exclude females over the age of 35 due to decreased fecundity.
‡ Current practice is to exclude cycles where vaginal intercourse did not occur or where additional nonhormonal or emergency contraception was used.
¥ Months of exposure calculated based on the number of actual use study days (AUSDs) divided by 28, where the number of AUSDs is based on FDA's analysis of the primary efficacy endpoint in ACCESS. Does not account for improbable dosing. Cycles were not excluded based on absence of intercourse or use of additional nonhormonal or emergency contraception.
§ One pregnancy occurred in a study participant (BMI 39.3) identified to be in the improbable dosing cohort.
€ CDC defines overweight as BMI of 25 to < 30 kg/m^2 and obesity as BMI ≥ 30 kg/m^2.
£ The Pearl Index was assessed as a secondary endpoint in ACCESS; the number of cycles and duration of exposure are less than would be expected in a contraceptive clinical trial. The PI lacks precision, as is evident when comparing confidence intervals for these estimates. Applicant analysis: PI = 2.2 with 95% CI (0.8, 4.8); FDA analysis: PI = 3.4 with 95% CI (1.6, 6.4); FDA analysis excluding improbable dosing: PI = 4.4 with 95% CI (1.9, 8.8).
Abbreviations: ACCESS, Adherence with Continuous-dose Oral Contraceptive: Evaluation of Self-Selection and Use; BMI, body mass index

While these PI estimates appear relatively low, major limitations of the data exist. Details of these limitations are discussed below.

Original NDA for Ovrette (norgestrel) Tablet 0.075 mg in 1973

Eight open-label, single-arm clinical studies provided data on the contraceptive efficacy and safety of norgestrel tablet 0.075 mg for initial approval in the prescription setting in 1973. These studies enrolled healthy premenopausal females between the ages of 15 and 49 years with regular coitus. The original clinical study population consisted of 53% females who identified as White, 47% Black, 0.3% Asian, and 0.1% Native American. A total of 1,950 females completed a total of 20,833 months of study drug use, and a total of 37 pregnancies were reported. These findings represented a PI of 2.3 per 100 woman-years. (For context, the PI for combined oral contraceptives approved around the same time were generally less than 1.0 per 100 woman-years.)

One should note the methodologic differences between the clinical study design used to determine effectiveness to support the original approval of Ovrette in 1973 compared to the design and conduct of contraceptive clinical studies deemed acceptable by current standards. Differences also exist in the methodology of the PI calculation between the original approval of Ovrette and recent contraceptive product approvals. Specifically, the original clinical studies for Ovrette included females over the age of 35 years who may be less fertile than those younger than 35 years, whereas current studies do not enroll females older than 35 years; study participants continued in the study for up to 5 years whereas current studies are approximately 52 weeks; and cycles where use of additional nonhormonal contraception (such as barrier contraceptives) were not excluded from efficacy analysis whereas such cycles would not be included in efficacy analyses in current studies. Additionally, calculation of the PI relied on months as the unit of measure for duration of exposure, as opposed to the number of cycles as the unit of measure in current practice, and CIs were not calculated at that time. Therefore, it is challenging to compare the efficacy of norgestrel 0.075 mg tablet as established at the time of approval to the efficacy of more recently approved oral contraceptive products.

Meta-analysis

At FDA's request, the Applicant submitted the meta-analysis of published studies from 1968 to 1993 to provide a current understanding of norgestrel 0.075 mg contraceptive effectiveness in today's U.S. population. However, the FDA review team disagrees with the methodology and conclusions of the meta-analysis submitted by the Applicant. The heterogeneity of study designs, populations, and length of the analyzed studies precludes meaningful conclusions about the efficacy of norgestrel tablet 0.075 mg in the current US population. Many of these studies were conducted in the 1960s and 1970s and several were conducted using populations outside the United States (ex-U.S.). Compared to the U.S., ex-U.S. populations have consistently demonstrated lower PI, which is likely due to differences in the populations studied. The studies cited in the Applicant's meta-analysis inconsistently reported methodologies. Additionally, small sample sizes and varying study durations make pooling of the available data from published literature over time unreliable. Finally, contraceptive clinical studies of longer than one year duration have been particularly problematic as they result in significant dilution of the PI and are not acceptable to demonstrate efficacy. Of the 8 studies the Applicant cited, 5 were longer than 1 year (13 cycles). Because the strength of a meta-analysis depends on the quality of the studies being analyzed, the FDA review team concludes that this meta-analysis does not provide new information regarding the efficacy of norgestrel tablet 0.075 mg in the prescription setting in the United States. Additionally, none of these studies provide effectiveness data that can be extrapolated to a nonprescription setting.

ACCESS Actual Use Study

The Applicant-reported PI in this study was 2.20 pregnancies/100 women-years based on 6 on-treatment pregnancies and up to 6 months of norgestrel tablet 0.075 mg use. However, data from this

study results in an imprecise estimate of the PI. The total number of cycles of exposure is significantly less than would be expected in a controlled contraceptive clinical trial. In ACCESS, participants contributed approximately 3500 cycles over 6 months. In comparison, recently FDA approvals of prescription oral contraceptives have required a minimum of 5000 cycles for a 6-month clinical trial or 10,000 cycles for a 1-year clinical trial. In addition, cycles were not excluded based on absence of intercourse or use of additional nonhormonal or emergency contraception, and use of other hormonal contraception is not accounted for. Furthermore, exclusion of the improbable dosing cohort would result in an even smaller denominator in an already underpowered study. In the FDA reviewers' analysis, the PI was 3.4 pregnancies/100 women-years based on a more conservative estimate of 9 on-treatment pregnancies.

Conclusion

In summary, the contraceptive efficacy of norgestrel tablet 0.075 mg as a prescription product has been established since the NDA's approval in 1973. Nevertheless, the FDA review team believes the dependence of contraceptive efficacy of this product, a POP, on strict adherence to the dosing regimen (once daily, every day, at approximately the same time each day), and increasing body mass index (BMI) in the U.S. population would likely impact real-world effectiveness of norgestrel tablet 0.075 mg if it were to be reintroduced in the prescription setting and also likely impact the real-world effectiveness of norgestrel tablet 0.075 mg in a nonprescription setting. The PI has gradually increased over time, likely due to several factors including increasing rates of obesity, potentially lower adherence to dosing regimens, and different study methodologies and counting rules (e.g., the use of transvaginal ultrasound for pregnancy confirmation has increased the number of confirmed pregnancies; the current definition of evaluable cycles has decreased the number of cycles available for analysis). FDA is not aware of any recent data (i.e., data in the last 20 years) on the contraceptive efficacy of norgestrel using more current clinical study design and conduct methodology. Further, typical use efficacy data with POPs are very limited; most typical use data for oral contraceptives are from use with combined (estrogen plus progestin) hormonal contraceptive products. Based on the mechanism of action, contraceptive efficacy of norgestrel relies more stringently on taking the tablet at approximately the same time each day for optimal efficacy compared to combined oral hormonal contraceptives. Therefore, the expected contraceptive efficacy of norgestrel tablet 0.075 mg as a nonprescription product is unknown.

3.1.2.2 Efficacy Issue #2: Potential Loss of Contraceptive Efficacy with Inconsistent Timing of Pill Intake

Taking norgestrel tablet at approximately the same time each day is essential for contraceptive efficacy because of the known pharmacokinetic (PK) properties of norgestrel and other oral progestins. The prescribing information for norgestrel tablet states that serum progestin levels are near baseline 24 hours after drug ingestion, making efficacy dependent upon rigid adherence to the dosing schedule. Progestin-only administration results in lower steady-state progestin levels and a shorter elimination half-life than concomitant administration with estrogens. (Opill USPI (2017)) As a result, the PD effects of norgestrel may dissipate rapidly if dosing is not repeated 24 hours after the previous dose. In addition, wide variations in serum progestin levels occur between individual users (Opill USPI (2017)In addition, wide variations in serum progestin levels occur between individual users (Opill USPI (2017)), making it impossible to predict who may be most susceptible to contraceptive failure. In contrast, combined hormonal contraceptives, which contain both a progestin and an estrogen, more reliably suppress the midcycle luteinizing hormone and follicle-stimulating hormone peaks as well increase circulating sex-hormone binding globulin, increasing steady-state serum progestin levels. As a result, ovulation is more reliably suppressed, resulting in more reliable contraceptive efficacy and less reliance on strict adherence to timing of daily dosing.

The Applicant voluntarily conducted Study 151042-002 (hereafter Study 002) to assess whether a delay in tablet intake would impact contraceptive efficacy based on PK/PD markers. The Applicant did not submit the protocol for FDA review or comment prior to study initiation. Study 002 was a prospective, multicenter, randomized, cross-over PK/PD study that evaluated the effect of norgestrel tablet 0.075 mg on cervical mucus and ovarian activity during perfect use (n=50 completed "perfect use cycle"), after one delayed intake of six hours (n=47 completed "delayed intake" cycle), and after a missed tablet (n=46 completed "missed pill" cycle). The Applicant also proposed a determination of "conception protection" based on a composite of cervical mucus and "ovarian activity" scores as an exploratory endpoint. (Refer to Section 5.9 for additional details).

The FDA review team concludes Study 002 is not appropriately designed to assess whether extending the time for norgestrel tablet intake affects contraceptive efficacy. Specifically, the FDA review team disagrees that the degree of "conception protection" can be obtained based solely on cervical mucus assessment and an "ovarian activity" scoring methodology, based on the following:

1. Neither cervical mucus scores nor "ovarian activity" scores are validated surrogate measures of contraceptive efficacy. In clinical development programs for contraceptive products, phase 2 PD studies using these types of exploratory endpoints may be supportive evidence for dose finding but are not sufficient in themselves to predict contraceptive efficacy or to inform appropriate timing of contraceptive dosing.
2. The "ovarian activity" scores used in this study are not validated measures of ovulation or delay of ovulation. FDA defines ovulation as a series of events documented by serial transvaginal ultrasounds coupled with serum estradiol and serum progesterone measurements. Delay of ovulation alone does not predict contraceptive efficacy as pregnancy may still occur if viable sperm are present in the female reproductive tract when ovulation occurs, albeit delayed. Thus, PD parameters alone are not sufficient to demonstrate that a delayed or missed tablet intake does not impact contraceptive efficacy.

Other limitations of Study 002 include:

- Applicant did not provide an assessment of the impact of levonorgestrel (LNG), the active ingredient of norgestrel, concentrations on cervical mucus at baseline.
- PK sampling of LNG did not correlate with known or expected changes in the PD such as cervical mucus quality. This raises significant questions about the value of the "ovarian activity" score.
- Cervical mucus and "ovarian activity" were not adequately assessed in overweight and obese females.

Conclusion

In summary, the FDA review team believes that measurement of "ovarian activity" and cervical mucus are insufficient as surrogates for contraceptive efficacy or to support changes in timing of dosing. Based upon the known PK properties of norgestrel, strict adherence to the recommended dosing regimen is needed to ensure contraceptive efficacy of norgestrel tablet 0.075 mg. (Opill USPI (2017))

3.1.2.3 Efficacy Issue #3: Efficacy in Females with Increased BMI

Recent approvals of hormonal contraceptives demonstrate a correlation between increasing BMI and decreasing efficacy of hormonal contraceptives (which includes oral and non-oral combined and progestin-only contraceptives). The exact mechanism of is unknown; one hypothesis is that increased volume of distribution associated with being overweight or obese results in decreased circulating concentrations of contraceptive hormones. Although contraceptive efficacy in the presence of overweight and obesity has not been specifically studied for norgestrel, recent PK data demonstrates

decreased circulating concentrations of progestins with increased BMI (Jatlaoui and Curtis 2016). Given that this product was approved in the 1970s and the paucity of data in today's target population of reproductive females in the United States, real-world effectiveness of this product in the United States remains ill-defined.

Although the original clinical trials for norgestrel tablet do not present data based on weight or BMI, the prevalence of obesity in adults in the United States has changed dramatically since the original clinical studies were conducted over 50 years ago. According to the CDC, the prevalence of obesity in adults in 1960 was approximately 13% (May et al. 2013), whereas the prevalence of obesity now is 42% (National Institute of Diabetes and Digestive and Kidney Diseases September 2021). Study 002 conducted by the Applicant had limited PD data in individuals who are overweight or obese. Nevertheless, the small sample size and lack of PK/PD correlation preclude conclusions regarding the impact of BMI on the efficacy of norgestrel tablet.

Conclusion

The efficacy of norgestrel tablet was established with its approval in the 1970s. Although the original approval of norgestrel tablet was based on data that was representative of the population likely to use the product at that time, the anthropometric changes within the target population over the past 50 years may impact the contraceptive efficacy of norgestrel today. The degree to which efficacy of norgestrel tablet is diminished in individuals who are overweight or obese (which together now represent approximately 60% of the U.S. reproductive-aged population (National Institute of Diabetes and Digestive and Kidney Diseases September 2021)) remains unknown. Neither Study 002 nor ACCESS provide additional insight into norgestrel's magnitude of contraceptive efficacy in the population likely to use the product in a nonprescription setting.

3.2 Consumer Behavior Studies Issues

3.2.1 Background on Consumer Behavior Studies

What is a Drug Facts Label, a Consumer Information Leaflet, and a Principal Display Panel?

In the nonprescription environment, where a healthcare intermediary such as a physician or pharmacist is not required to be involved in consumer decision-making, the relevant information about a drug is described to consumers in the DFL. DFLs need to adhere to regulatory requirements for standardized content and format[1]. DFLs must appear on the outside container or wrapper of the retail package; if there is no outside container or wrapper, it must be on the bottle or other applicable container.

Each DFL must contain a Drug Facts title, description of the active ingredient(s), purpose(s) (principal intended action); indications ("Uses"); warnings (including but not limited to "do not use" – or absolute contraindications), "ask a doctor before use if you have", "ask a doctor or pharmacist before use if you are", "when using this product", stop use and ask a doctor if" and any other applicable warnings; directions for use; other information., inactive ingredients. Other aspects of the DFL regulation include type size, style, spacing, and use of bolding.

Although the DFL must provide all critical information necessary for safe and effective use of the product, a CIL may be provided inside the package to include supplementary use information.

[1] The standardized content and format is described in the Code of Federal Regulations found under 21CFR 201.66.

In addition to the DFL and any relevant CIL, the principal display panel (PDP) is also considered to be labeling. The PDP is that part of the label that is most likely to be displayed and examined by consumers at the point of sale – the outer package. At times, critical information on the DFL may also be restated on the PDP[2], so that it is able to catch consumers' attention at the point of sale. Additionally, any wording on the inner blister pack (pre-formed plastic packaging in which tablets are individually sealed) is also considered to be labeling. The blister pack is subject to four mandatory requirements for small labels which include: the proprietary name of the drug; the established name (if there is one); an identifying lot or control number; and the name of the manufacturer, packer, or distributor of the drug. An Applicant can also utilize a blister pack to reinforce selected key DFL statements by reiterating them on the pack, since the consumer will see it every time they use the medicine.

The proposed carton labeling (PDP and DFL), CIL, and blister pack for this product are in Sections 5.1, 5.3 and 5.5.

What is a Label Comprehension Study?

LCSs are conducted for virtually all new prescription to nonprescription switch NDAs. These studies are designed and conducted based on recommendations in an FDA Guidance for Industry (August 2010). Label comprehension is foundational in a nonprescription drug development program, to determine if the DFL and CIL (if applicable), successfully communicate important information about a drug to ultimately facilitate the safe and effective use of the drug.

In an LCS, applicants need to identify the most important communication objectives that need to be assessed as primary objectives. These are the most important concepts, from the viewpoint of safety and efficacy, that need to be understood by consumers. Target thresholds are established a priori and are based on clinical implications if consumers fail to adequately understand the labeled items. For instance, for a hormonal contraceptive product, a target threshold for comprehension of "do not use if you have or ever had breast cancer" could be established at 90%, because there would be serious medical consequences for the consumer with breast cancer if the consumer were to use the product.

Adequate comprehension is assessed by comparing the established threshold with the lower bound of the two-sided exact 95% CI (LB) for the comprehension rate. For example, if the LB is 92% and the target threshold is 90%, adequate comprehension would be demonstrated. If the LB is 84% and the target threshold is 90%, adequate comprehension would not be demonstrated. The lower bound is utilized because it accounts for the uncertainty in the estimate of the comprehension rate. Typically, LCSs have multiple primary endpoints and are designed to assess comprehension of all primary endpoints.

It is important to note that in nonprescription consumer behavior studies, success thresholds are targets—and not automatic "hard stops." If an objective fails to meet a threshold, the clinical impact is considered within the overall benefit-risk assessment.

FDA typically asks applicants to include approximately one-third limited literacy representation in their consumer studies, reflecting estimated proportions in the population based on the 2003 National Adult Assessment of Literacy. Generally, participants in consumer studies are administered the Rapid Estimate of Adult Literacy in Medicine (REALM) test, which is a validated literary assessment tool. For the purposes of nonprescription regulatory consumer studies, limited literacy is defined as scoring <60 on the REALM test, which represents a reading level of eighth grade or below.

[2] The labeling of all nonprescription products must display the statement of identity on the drug product's PDP (21 CFR 201.61).

Secondary communication objectives are intended to address areas less critical, but still clinically relevant, to safe and appropriate use. Secondary communication objectives typically are not assessed against target thresholds.

LCSs usually enroll as demographically diverse a population as possible. Generally, the studies include 300 to 600 participants from a variety of marketing research sites across the United States. These studies (and all consumer behavior studies described in this section) utilize convenience samples rather than statistically rigorous probability sampling. Typically, LCSs are conducted with "all comers"; they are usually intentionally not limited to sufferers of a condition, because anyone should be able to pick up a DFL and/or a consumer information leaflet and understand what it says. Also, consumers can develop a need for a product in a therapeutic category that is new to them.

In an LCS, consumers are given the DFL to read at their own pace. They are then asked questions about the label and can refer back to it as much as they want. It is not a test of memory, but rather an "open book" test to assess whether consumers are aware of and can understand key elements presented in the DFL. Questionnaires need to be constructed targeting the communication objectives in an unbiased way. LCSs typically employ many scenario questions, describing hypothetical consumers and their medical situations in order to test the ability of the consumer to apply the information from the label.

Ultimately, LCSs assess comprehension, and not consumer behavior. Therefore, LCSs are usually necessary as the foundation of successful nonprescription development programs. If a proposed label does not facilitate sufficient comprehension by consumers, it is far less likely that consumers would then be able to correctly self-select and use the product in a safe and efficacious manner. Ideally, LCS provides a foundational opportunity to optimize the label before any other necessary studies are conducted.

What is a Self-selection Study?

Self-selection studies assess whether consumers can apply their understanding of the label to their own personal medical situation for making a drug use decision. These studies are based upon FDA's Guidance for Industry: Self-Selection Studies for Nonprescription Products (April 2013) (Self-Selection Guidance). Endpoints are determined by FDA's clinical concerns; they may focus on correct targeted deselection among a population of clinical concern and/or correct self- FDA selection with a general population.

Targeted Self-selection (Deselection) Study

Typically, FDA might require a study when there is a potential concern about a specific subpopulation using the product, as for instance, in the case of norgestrel, women who have or have had breast cancer. FDA is interested in consumer research demonstrating that this subpopulation would not self-select to use the product at all, since the DFL contains the warning "Do not Use." This type of self-selection study is also characterized as a "deselection" study.

Targeted self-selection/deselection studies are important because some consumers might "understand" a label in the abstract - as demonstrated in label comprehension - but not always understand that they personally have a condition that could preclude them from using the drug. Applicants need to assess the extent to which the relevant consumers can understand this deselection criteria on their own, since they would have unrestricted access to a product in the nonprescription environment, rather than through the "gatekeeper" of a healthcare practitioner. Therefore, correct deselection is a way of validating the label. Target thresholds for the critical deselection endpoints are established a priori based on the clinical implications of failure of users to correctly self-select. Target LB thresholds for deselection studies are typically 90%, reflecting the clinical importance of consumers to adhere to "Do not Use" warnings, although the target threshold may be set higher or lower depending on the clinical risks involved with failure to deselect. As with label comprehension studies, if a threshold falls below target,

that does not mean that approvability of the product is automatically negated; rather, it is carefully considered as part of the benefit-risk assessment.

In targeted self-selection studies/deselection studies, consumers are recruited for a specific contraindicated condition or medication, or another specific "do not use" category, such as age or gender. The participants themselves are usually "blinded" to why they are being recruited. Recruitment may take place through advertisements, research site facility databases, medical offices, and pharmacy benefits databases.

Targeted self-selection/deselection studies sometimes involve less than an ideal number of limited literacy participants, because it is sometimes more difficult to recruit for participants who self-report – and are interested in discussing - specific medical conditions. While FDA recommends adequate limited literacy representation in the targeted self-selection studies, similar to that of LCSs, depending upon the medical condition of concern, sometimes targeted self-selection limited literacy representation is in the 15% to 18% range due to recruiting difficulties.

General (Non-targeted) Self-Selection and Deselection Studies

FDA sometimes wants to see if a general population, with a broad variety of medical conditions, will correctly choose whether or not to use a particular proposed drug based on the DFL statements about these conditions. Self-selection and deselection among a general population is sometimes conducted as a stand-alone study and sometimes conducted as an up-front component to an actual use study. For a non-targeted self-selection study, the LB threshold for the correct selection endpoint is typically 85%.

Design and Conduct of Self-selection Studies

In self-selection studies, participants are given the proposed product package with the DFL, asked to look at it as if they would do if potentially interested in using a drug, and then tell the interviewer whether the drug would be appropriate or not for them personally to use, given their health conditions. Per the Self-Selection Guidance (2013), the recommended self-selection question is: "Is it okay for you to use this medication", followed by open ended probing questions such as "why do you say that?." Often to validate whether participants have selected appropriately with respect to contraindicated medical conditions or other drugs, the participants are then interviewed after their selection decision by a physician or other health care professional. The health care professional may administer tests, as well as obtain a detailed medical history to assess the appropriateness of the selection decision. Medical history questions are asked after the self-selection question to prevent bias because of prompting participants to focus on particular aspects of the label when making their self-selection decision. Medical history questions can be utilized to validate the self-selection decision.

The Self-Selection Guidance (2013) goes on to state that sponsors sometimes choose to add a question asking participants whether they would purchase the drug product, but that FDA does not consider purchase decision data to be a reliable surrogate for self-selection data because a purchase decision may be influenced by factors other than personal health history. If a sponsor wishes to collect data on purchase decision, these questions should be asked only following the completion of the self-selection portion of the assessment.

As the self-selection data are analyzed, study participants are classified into one of four cells (Table 2).

Table 2. Two-by-two Table of Cells of Participants in Self-Selection Study

Self-Selection Population	Appropriate to Use	Not Appropriate to Use
Selector	Cell A	Cell B
Non-selector	Cell C	Cell D

Source: Reviewer's Table adapted the table in FDA Guidance for Industry Self-Selection Studies for Nonprescription Drugs (2013)
Cell A comprises participants who select to use the product, and who are classified as medically appropriate to use.

Cell B comprises participants who select to use the product and who are classified as not medically appropriate to use.
Cell C comprises participants who do not select to use the product for whatever reason, and who are classified as medically appropriate to use.
Cell D comprises participants who do not select to use the product and who are classified as not medically appropriate to use.

Study endpoints are then derived from equations utilizing these cells. As noted, FDA often considers correct deselection rather than correct selection to be the most important endpoint, as that addresses safety. The deselection endpoint is most critical as it answers FDA's typical question: of all participants for whom the product is not medically appropriate to use, what percentage would have chosen to use the product in an in-market situation?

As per the Self-Selection Guidance (2013), the primary endpoint for a targeted deselection study is calculated as D/(B+D), which represents the proportion of participants who incorrectly selected to use the product out of the total who were inappropriate to use the product.

As for correct selection, the Self-Selection Guidance (2013) offers two possible equations calculating the endpoint of a correct self-selection study. One example is correct self-selection for the entire population, calculated as (A+D)/(A+B+C+D). Alternatively, the correct self-selection endpoint can be a calculation among those who select to take the drug A/(A+B).

What is an Actual Use Study (AUS)?

In an AUS study, participants actually take the study drug home for use and therefore, the study captures data on consumer behavior**.** Unlike an LCS or targeted self-selection study, an AUS is a type of interventional study because consumers are exposed to the study drug. The purpose of an AUS is to simulate the nonprescription use of a product and in doing so, provide meaningful consumer data to predict if a drug will be used properly, safely, and effectively in a "naturalistic" nonprescription setting. Some AUS studies also include a self-selection component. Examples of elements an AUS can assess are:

- Correct deselection among the general population (if there is an up-front self-selection component).
- Correct selection among the general population (if there is an up-front self-selection component).
- Adherence (taking the drug and performing any monitoring for efficacy and safety in accordance with the drug label).
- Safety (adverse events [AEs] that occur during the study).
- Safe use behavior (correct stopping of drug or seeking help from a medical professional, e.g., if an AE occurs).
- Effectiveness (whether the clinical benefit in the prescription setting is reproduced in the nonprescription setting).

AUSs can assess the ability of the consumer to use the product for the indicated purpose (self-treat) and can also assess whether consumers are abusing or misusing the study drug. Some issues that might trigger the need for an AUS include concerns about adherence to dosing directions to achieve efficacy; concerns about excess dosing and potential misuse that could lead to safety issues; and adherence to "stop use and ask a doctor" warnings.

Study Design: the design of an AUS can vary depending on the type of product studied and the intended use. Usually, an AUS is a single-arm, multi-center, uncontrolled, open-label design. Ideally, all consumers who may have an interest in using the product should be the target of recruitment efforts. An AUS should be conducted in a manner that simulates, as closely as possible, the true nonprescription environment. While a truly "naturalistic" environment that replicates the nonprescription setting cannot be perfectly achieved, the AUS provides simulated data for assessment.

Self-selection studies as an up-front component of an AUS present special design and analytical challenges. These are fielded when more data are needed about how the general population would self-select to use the product, in somewhat of a realistic setting where they know they could actually use the product. However, the necessity of a medical interview and pregnancy test (where applicable) to determine the accuracy of their selection decision, as well as to exclude anyone with a contraindication, serves to make the study less naturalistic. Other study elements that can limit the naturalistic setting are the informed consent form, and data collection tools such as diaries and interim study nurse interviews, which can serve as memory prompts to the participant but not carry over to a real world in-market scenario. Nonetheless, if study participants can purchase the study drug typically without restriction, and if there is no unsolicited HCP involvement, a study can come somewhat close to approximating a real-world nonprescription purchase setting and provide useful selection and actual usage data.

It is common that an AUS has multiple primary endpoints and is designed to assess success of all primary endpoints. The acceptable success rate for pivotal issues related to actual use for a nonprescription product is discussed during drug development with industry sponsors. Acceptable error depends upon the specific drug, specific indication, and safety concerns. Consideration is given to how best to collect data to allow decisions on approval of a drug, especially when a small percentage of users could potentially be harmed by inappropriate use. The success of consumer behavior studies considers the totality of the results of the study and, generally, the success or failure on a particular endpoint is not considered a definitive marker of the success of the study. Understanding why consumers failed on a particular endpoint can provide valuable information on steps that can be taken to improve appropriate use. However, failure to achieve endpoints, especially primary endpoints, raises concern regarding whether consumers will be able to correctly deselect or use a product as directed.

Consumer Study Summary

Below are key takeaways from the overview of consumer behavior studies in the nonprescription regulatory environment:

- In the nonprescription environment there is no gatekeeper. Consumers need to be able to understand “do not use” and other absolute and relative contraindications on their own and make decisions accordingly without assistance from a learned intermediary.
- Label comprehension studies assess comprehension and not behavior. They are generally considered to be necessary, but not sufficient, barometers of safe and efficacious use.
- Self-selection studies assess consumers’ assessments about whether a product is appropriate for them to use based on their own medical history. They are not intended to incorporate an actual purchase decision in that assessment, because purchase depends on other factors, including an actual need for the product at the time and/or whether the consumer is already satisfied with their current treatment.
- Targeted deselection studies are the most important type of self-selection study because they focus on only those consumers for whom a product is inappropriate to use. Those thresholds typically set based on a LB of 90%. (General self-selection studies are another type of self-selection study, focusing on all consumers who might be interested in using a product. Those thresholds are typically LB of 85%).
- Target thresholds for all studies are established a priori and reflect the most important concepts that consumers need to understand, based on the clinical implications of failure to understand (such as a contraindication or important direction for use impacting efficacy). Generally, the most important primary endpoints incorporate target thresholds of 90%, which means that the lower

bound of the two sided exact 95% CI for the comprehension rate or the selection rate needs to meet or exceed 90%.

- In general, FDA asks for approximately one third of the study population for each consumer study to be of limited literacy, reflecting published estimates of limited literacy representation in the general population.
- In an AUS study, participants take the study drug home for use. The purpose of an AUS is to simulate the nonprescription use of a product and in doing so, provide meaningful consumer behavior data to predict if a drug will be used properly, safely, and effectively in a "naturalistic" nonprescription setting.

3.2.2 Consumer Behavior Studies Submitted by Applicant

Table 3 provides an overview of the pivotal consumer behavior studies submitted by the Applicant and discussed in detail in this briefing document. The OPTION study is not included since it was terminated early due to failure of the medication use e-diary. The safety data from this study is included in Section 3.3.2.

Table 3. Overview of Consumer Behavior Studies Discussed in Section 3.2.2

Study Type	Study Name (Conduct Period)	Study Objective	Study Design	Number of Participants	Labeling Used
Label comprehension for Drug Fact Label (DFL)	Study to Test the Self-Selection and Comprehension of the Opill® OTC Drug Facts Label (July 2021 to September, 2021)	To evaluate if important messages in DFL were adequately comprehended	Single visit, virtual interview	477 participants in LCS-only cohort: 32% 11-17 years old, 26% Limited Literacy	Earlier version of proposed DFL (Version G)*
Label comprehension for Consumer Information Leaflet (CIL)	Multicenter Study to Test the Comprehension of Messages on the Opill® OTC Consumer Information Leaflet (July 2017 to August 2017	To evaluate if the key messages in CIL were adequately comprehended	Single visit, in-person interview; multicenter	551 participants: 27% 11-17 years old, 25% Limited Literacy	Earlier version (2017) of proposed CIL
Targeted Self Selection for Breast Cancer	Study to Test the Self-Selection and Comprehension of the Opill® OTC Drug Facts Label (July 2021 to September 2021)	To evaluate whether women with a history of breast cancer could correctly determine, using only the nonprescription DFL, that norgestrel was not appropriate for them to use	Single visit, virtual interview	206 in self-selection only cohort: 53% 25-45 years old, 47% 46+ years old. 5% Limited Literacy	Earlier version of proposed DFL (Version G)
Self-Selection Component of Actual Use Study	Adherence with Continuous Dose Oral Contraceptive: Evaluation of Self-Selection and Use (ACCESS) (September 2019 to August 2021))	To evaluate the adequacy of the proposed nonprescription labeling to guide appropriate consumer selection.	Single visit, single arm, non-randomized open-label multicenter study	1772 in self-selection population: 21% 11-17 years old, 13% Limited Literacy	Earlier version of proposed DFL (Version F), which contained “DNU” for all cancer (currently only DNU for breast cancer in Version G and H)

Study Type	Study Name (Conduct Period)	Study Objective	Study Design	Number of Participants	Labeling Used
Use Component of Actual Use Study	Adherence with Continuous Dose Oral Contraceptive: Evaluation of Self-Selection and Use (ACCESS) (September 2019 to August 2021)	Evaluate the adequacy of the proposed nonprescription labeling to guide appropriate consumer use behavior	Single arm, non-randomized, open-label, multicenter 24-week study Hybrid of on-site and virtual due to COVID-19	883 in User Population: 23% 11-17 years old, 14% Limited Literacy	Earlier version of proposed DFL (DFL Version F) and 2017 version of proposed CIL

Source: Created by FDA review team from data provided in the Applicant's submission of NDA 017031 S-041.
Note: The Study to Test the Self-Selection and Comprehension of the Opill® OTC Drug Facts Label was a combined label comprehension and targeted breast cancer selection study.
Abbreviations: COVID-19, coronavirus disease 2019; DNU, do not use; LCS, label comprehension study; OTC, over-the-counter; ACCESS: Adherence with Continuous Dose Oral Contraceptive: Evaluation of Self-Selection and Use; Targeted Breast Cancer Self Selection Study: TBCSSS

Labeling Utilized in Consumer Studies

The ACCESS study utilized an earlier version of the DFL; the Applicant refers to this as Version F. A later version, DFL Version G, was used in the TBCSS/LCS. DFL Version H is the DFL submitted in the sNDA.

Notable changes made to the proposed DFL after the ACCESS study include:

- The statement "Ask a doctor before use if you have unexplained vaginal bleeding between your periods" was changed to delete the word "unexplained" and to add "and you have not already talked to a doctor"
- The change of the do not use "if you have ever had any cancer" warning to do not use "if you have or ever had breast cancer."
- The warning pertaining to "you have or ever had any cancer" was moved from the do not use section to the ask a doctor before use section.
- The warning regarding ectopic pregnancy was changed from "talk to a doctor if you have sudden or severe pain in your lower belly—see a doctor immediately (you could have an ectopic pregnancy)" to "Seek medical help right away if you have sudden or severe persistent pain in your lower belly mostly on one side (you could have an ectopic pregnancy)."
- Both the DFL used in the ACCESS study (DFL Version F)) as well as the proposed DFL submitted in this sNDA package (DFL Version H) listed instructions on when to use a condom (or another barrier method). However, the DFL which was used in ACCESS listed these instructions only in the "Directions" section of the DFL while the DFL submitted in the sNDA package (DFL Version H) listed instructions of when to use a condom (or another barrier method) in the "Directions" section as well as in an additional section titled "When to use a condom (or another barrier method)." The DFL that was revised after the completion of ACCESS (DFL Version G) was subsequently tested in the combined LCS/Targeted Breast Cancer Self-Selection Study.

Differences between DFL Versions G and H include the following:

- The word "unexplained" was added back into "Ask a doctor before use if you currently have unexplained vaginal bleeding between your periods and you have not already talked to a doctor".

- The message “You should continue to see your healthcare provider for routine healthcare visits” was moved from the “Other Information” section to the “Directions” section
- The order in which the statements in the “Other Information” section were listed was changed.

3.2.2.1 Drug Facts Label (DFL) Comprehension Study

Overview

The objective of the DFL LCS was to evaluate if the important messages in the currently proposed DFL were adequately comprehended. The LCS was a single virtual-visit study designed to evaluate comprehension of the currently proposed DFL for norgestrel tablet among females ages 11-50 years. This LCS study was designed by the Applicant as a combined targeted breast cancer self-selection/LCS study. Because those who responded “yes” to the question of history of breast cancer were no longer naïve to the DFL (see Section 3.2.2), the FDA review team focused only on those who responded “no” to a history of breast cancer in the self-screening questionnaire as these participants were not exposed to any discussion of the DFL prior to the assessment for comprehension of the DFL. We refer to this as the LCS-DFL. This study group consisted of 477 participants, 26% of whom were of limited literacy.[3]

There were 14 primary endpoints with prespecified LB target thresholds of 90% for each endpoint. The primary endpoints were the DFL statements of the highest levels of clinical importance to either safety or efficacy. To demonstrate successful comprehension, the final LCS protocol stated that the lower bound of the target threshold would have needed to be met on all 14 primary endpoints. The lower bound of the target threshold was not met on 7 of the 14 primary endpoints.

The study findings suggest that consumers do not adequately understand some of the necessary actions they need to take if they miss a tablet (such as the need for condoms or other barrier contraception) in order to avoid unintended pregnancy. Findings also show that consumers confuse the absolute contraindication – do not use- if they have breast cancer - with the relative contraindication of asking a doctor if they have any cancer. Consumers also confuse the need to ask a doctor before use if having unexplained vaginal bleeding with other vaginal bleeding scenarios during use.

Results further demonstrate confusion about the difference between norgestrel and an emergency contraceptive.

Methods and Analysis

The sample size was determined by precision of the estimate. Assuming a 92.5% correct response rate, a sample of 475 participants was expected to have a 95% exact CI with a width of approximately ±2.5%.

[3] Administering the REALM and REALM-Teen virtually is a novel approach and was employed by the Applicant during the conduct of this study in part due to COVID-19 pandemic related considerations. We note that in the published literature (Aker, JL, TC Davis, A Leonard-Segal, L Christman, S Travis, M Beck, and A Newton, 2022, Evaluating Health Literacy in Virtual Environments: Validation of the REALM and REALM-Teen for Virtual Use, J Gen Intern Med, 37(11):2834-2839. there is an assessment of the validity of the REALM and REALM-Teen for virtual use. These published results, based on a study that included participants with smartphones, laptops, and desktops, appear to tentatively support validity in adults while the results in adolescents are less robust. However, the Applicant conducted this study with an upfront exclusion of anyone who did not have access to a desktop or laptop for the study. The Applicant did not provide documentation to support the validity of this approach. Therefore, the extent of validity of the Applicant’s REALM results to both the adult and adolescent populations is unclear.

Each comprehension rate was computed as the number of participants with an overall correct response divided by the number of participants in the analysis population. Two-sided 95% CIs were computed using an exact method (Clopper-Pearson). A primary endpoint is successful if the lower bound (LB) of the 95% CI was equal to or greater than the pre-specified threshold of 90%.

The LCS analysis population was defined as all participants who were not asked to make a self-selection decision and answered at least one comprehension question. This LCS study was originally designed as a combined targeted breast cancer self-selection/LCS study. Participants in this study had a history of breast cancer, had undergone the TBCSS interview first, then administered the LCS (see section 3.2.2). However, since the TBCSS participants were at that point not naïve to the label and the breast cancer warnings, FDA reviewers decided to focus on the LCS-only participants for the DFL LCS —that is, the 477 who entered the LCS without prior exposure to any discussion or exposure to the DFL.

FDA reviewers conducted an independent qualitative analysis of the participants' individual verbatim responses to each of the study questions. Based on that analysis, FDA reviewers recalculated four primary endpoints and nine secondary endpoints. None of the primary endpoints changed substantially because of the recalculations, but the in-depth review enabled reviewers to gain insights into areas of participant confusion, where applicable, regarding some of the DFL statements. A complete listing of all study endpoints is found in Table 11.

Study Results

Demographics

The median age was 26, and adolescents comprised 32% of the study population. Of the participants, 58% self-reported that they were white, 29% were black, and 15% Asian. Regarding prior contraceptive use, 47% had previously used an oral contraceptive, 10% had used another form of hormonal birth control and 43% had no previous hormonal birth control use. See Section 5.10, Table 10 for additional details.

Results

DFL statements not well understood by consumers

There were a number of important endpoints related to comprehension of DFL statements focusing on self-selection and usage that did not approximate the target threshold of 90%.

Do not Use with breast cancer

- Statement: "Do not use if you have or ever had breast cancer"
  - Results: comprehension [84%, 95% CI (80%, 87%)].
    - Among participants aged 18 years and older, comprehension of this endpoint was only 79%, 95% CI (75%, 84%).
  - The Applicant's analysis of this endpoint was 88%, 95% CI (84%, 90%).
  - An analysis of the incorrect responses revealed that there was confusion with the other DFL statement to ask a doctor before use if you have or ever had any cancer (see Table 12 in the Appendix).

Ask a doctor if unexplained vaginal bleeding

- Statement: "Ask a doctor before use if you currently have vaginal bleeding between your periods and you have not already talked to a doctor"
  - Results: comprehension [86%, 95% CI (83%, 89%)].

- The Applicant's analysis of this endpoint was 93%, 95% CI (90%, 95%).
- Incorrect responses depicted participants who confused this statement with other statements on the label related to vaginal bleeding (see Table 13 in Section 5.10).

Use as an emergency contraceptive

- Statement: "Do not use as an emergency contraceptive (morning after pill). This product does not prevent pregnancy when used after unprotected sex"
  - Results: comprehension [76%, 95% CI (71%, 79%)].
  - The Applicant did not make this a primary endpoint, even though FDA had directed the Applicant to do so during the development program. (Note: the Applicant-reported secondary endpoint was 74%, 95% CI (70%, 78%).
  - Participants with incorrect responses tended to assume the question was referring to actions that needed to be taken after missing a tablet.

When to use a condom or other barrier method: Every time you have sex for the next 2 days (48 hours)

- Statement: "After you start your first pack of this product, because it takes 2 days for this product to start working"
  - Results: comprehension [87%, 95% CI (84%, 90%)].
- Statement: "If you are more than 3 hours late taking your tablet or miss taking your tablet on one or more days, because it takes two days for this product to start working again"
  - Results: comprehension [83%, 95% CI (80%, 87%)].
- Statement: If you vomit for any reason or have severe diarrhea within 4 hours of taking your daily tablet, because the medicine may not have been fully absorbed
  - Results: comprehension [85%, 95% CI (82%, 88%)].

DFL statements well understood by consumers

For other DFL statements, comprehension either exceeded or closely approximated the target threshold of 90%. These primary endpoints included:

- Take one tablet every day [99%, 95% CI (98%. 100%)].
- Take one tablet at the same time every day [98%, 95% CI (96%, 99%)].
- Do not use together with another birth control pill, vaginal ring, patch, implant, injection, or an IUD. [94%, 95% CI (90%, 96%)].
- To prevent pregnancy, take this product every day, even when you bleed or have spotting. [96%, 95% CI (94%, 98%)].
- When you finish this pack, start the next one the following day without a break [92%, 95% CI (89%, 94%)].
- If you are more than 3 hours late taking your tablet or if you miss taking your tablet on one or more days, take one tablet immediately, as soon as you remember it [97%, 95% CI (95%, 98%)].
- Seek medical help right away if you have sudden or severe persistent pain in your lower belly mostly on one side (you could have an ectopic pregnancy) [94%, 95% CI (91%, 96%)].

- Seek medical help right away if you develop yellowing of your skin or whites of your eyes especially with fever, tiredness, loss of appetite or dark colored urine [98%, 95% CI (96%, 99%)].

Assessment of Important Subgroups

The FDA reviewers performed additional subgroup analyses on the findings for two specific subgroups of concern – adolescents, and those of limited literacy. Of note, the percentage of LCS participants with limited literacy, at 26%, was lower than the estimated representation in the U.S. population. Therefore, the overall study may overestimate comprehension, as limited literacy subpopulations tend to exhibit worse comprehension than normal literacy overall.

In general, older adolescents had comparable comprehension to adults. However, younger adolescents ages 11 to 14 years scored lower than the age 15 to 17 and age 18+ years subgroups on several endpoints relevant to correct usage, such as in differentiating this product from an emergency contraceptive product and understanding some of the important directions, particularly in understanding when to use back up contraception and when finishing a pack, the need to start the next pack the following day without a break.

Adolescents ages 11-14: Comprehension Compared to Older Adolescents and Adults

- Statement: "when you finish this pack, start the next one the following day without a break.
  - Results: comprehension 78% versus 96% and 94% respectively.
- Statement: "Do not use as an emergency contraceptive (morning after pill). This product does not prevent pregnancy when used after unprotected sex"
  - Results: comprehension 57% versus 73% versus 80% respectively

Use a condom or other barrier method every time you have sex during the first 2 days of use (48 hours):

- Statement: "after you start your first pack of this product, because it takes 2 days for this product to start working"
  - Results: Comprehension 80%[4] point estimate (PE) versus 94% and 87%, respectively.
- Statement: "if you are more than 3 hours late taking your tablet or miss taking your tablet on 1 or more days"
  - Results: comprehension 66% versus 89% and 86% respectively.
- Statement: "if you vomit for any reason or have severe diarrhea within 4 hours of taking your daily tablet because the medicine may not have been fully absorbed"
  - Results: comprehension 74% versus 92% and 86% respectively.

Limited Literacy Comprehension of Important DFL Statements

- Statement: "Do not use as an emergency contraceptive (morning after pill). This product does not prevent pregnancy when used after unprotected sex"
  - Results: comprehension by normal literacy 81%, by limited literacy 56%.

[4] Results for the overall study populations are reported in point estimate and the 95% confidence interval. Results for subgroup analyses are reported in point estimates, as the sizes of some subgroups are small.

When to use a condom (or another barrier method): Every time you have sex for the first 2 days (48 hours):

- Statement: “if you are more than 3 hours late taking your tablet or miss taking your tablet on 1 or more days”
  - Results: comprehension by normal literacy 88%, limited literacy 71%.
- Statement: “if you vomit for any reason or have severe diarrhea within 4 hours of taking hour daily tablet”
  - Results: comprehension by normal literacy 90%, limited literacy 71%.

LCS Conclusion

In summary, participants demonstrated strong comprehension of key messages regarding directions for use—once a day, at the same time every day, transition to the next pack, and when to seek medical help right away. Moreover, participants demonstrated strong comprehension of the actions needed if a pill is missed—namely, to take it immediately, as soon as you remember it. In contrast, there seems to be a lack of adequate understanding as to the need for using back up contraception for the next 48 hours when a tablet is missed. Also of concern is the lack of adequate understanding that backup contraception is needed for the first 48 hours after starting use if having sex. Complete knowledge of what to do if a tablet is missed is an important aspect of efficacy since that may occur many times during a user’s reproductive years. The lack of understanding of the need for back up is concerning with regard to the potential for unintended pregnancies.

Regarding comprehension of correct deselection, it appears that there is consumer confusion between the DFL statements of “do not use” with current/past history of breast cancer and “ask a doctor before use” for all other types of cancers. A concerning number of participants overlooked the “do not use” and instead applied the “ask a doctor before use” to a scenario of breast cancer. It is of critical importance for all nonprescription DFLs that consumers understand that “do not use” is to be literally comprehended. Given that many consumers do not always have immediate access to a physician who knows their medical history, it is of vital importance that consumers understand on their own an absolute contraindication.

There is also confusion about what to do about unexplained vaginal bleeding. It appears that many participants confused various types of unexplained vaginal bleeding with the actions that needed to be (or not be) taken.

The comprehension of norgestrel in relation to other contraceptive methods is mixed. Based on the LCS, there appears to be a strong understanding that norgestrel should not be used together with other hormonal contraceptive methods. However, it appears that there is the potential for confusion between norgestrel and emergency contraception. This confusion is more pronounced in limited literacy and adolescent participants.

3.2.2.2 Consumer Information Leaflet (CIL) Comprehension Study

Overview

To evaluate the CIL, the Applicant conducted a single-visit, multi-center label comprehension study (LCS) from July- August 2017. The study included a total of 551 unique participants, ages 11 and older. The study was based upon a previous version of the currently proposed Consumer Information Leaflet (CIL) (Section 5.11). The objective of the CIL LCS was to evaluate if the key messages in the proposed CIL were adequately comprehended.

- Comprehension of some important CIL statements was strong regarding various aspects of usage but was not strong regarding two important statements that only appeared on the CIL - and were not reinforced on the DFL - due to DFL space limitations:
- If you are switching from another birth control pill, vaginal ring, or patch, start taking Opill the day after you stop the other method, and What if I have taken an emergency contraceptive before starting Opill?
- Also, use a condom (or another barrier method) every time you have sex until your next period.
- Moreover, as in the DFL Comprehension Study, there appeared to be confusion between norgestrel and emergency contraceptives.
- Because of the limitations of the design of the study (see Methods and Analysis), the FDA review team cannot conclude whether the study findings successfully demonstrated consumers understood the important messages in the CIL.

Methods and Analysis

The Applicant did not prespecify any primary endpoints in the LCS for the CIL. This is of concern because there were important messages on the CIL related to usage that were not reinforced on the DFL. Without having pre-specified primary endpoints in the testing of the CIL, there were no pre-specified thresholds in this CIL study, and it is therefore difficult to determine whether the study was successful in demonstrating that consumers understood the important CIL messaging.

The Applicant contends that because all information contained in the CIL is supplementary to the DFL, there was no need to designate primary endpoints with corresponding performance thresholds. The FDA reviewers do not agree that all information on the tested CIL, and on the proposed CIL, is purely supplementary.

As with the DFL LCS, the reviewer analyzed all of the qualitative verbatims on responses to the LCS for the CIL to gain insights as to why comprehension may not have been optimal.

Participant Demographics

The study population was comprised of 511 participants, 87% females and 13% males. Self-reported Whites comprised 62%, Blacks 25%, and Asians 1% of participants. Self-reported Hispanics comprised 21% of the study population. Adolescent females (ages 11-17) comprised 27%; the median age of the participants was 24. There were 136 (27%) participants of limited literacy. Refer to Table 14 (Appendix 5.11) for additional information.

Study Results

As a result of an in-depth analysis of the verbatims, FDA reviewers' analysis of the data yielded different results than the Applicant for 5 out of 12 endpoints (see Table 15, which summarizes the results for 12 endpoints). However, there was only one substantial change in comprehension of a CIL statement as a result of the FDA recalculation:

> What changes to my menstrual period are NOT expected when using Opill? Talk to a doctor while continuing to take this product every day even if you experience any of the following: You repeatedly have bleeding that is brought on by sex." FDA analysis of comprehension was 82% (95% CI 79%, 86%). The Applicant-reported comprehension was 93% (95% CI 91%, 95%). Many participants did not articulate in their response that a person should continue to take this product every day while in the process of seeking a doctor's advice. As comprehension of that concept is critical for efficacy, FDA reviewers did not consider those responses acceptable.

Comprehension of the following CIL statements was high:

- Statement: Continue taking Opill exactly as directed even if you have the following changes in your periods: your periods may be less or more frequent, shorter or longer, lighter or heavier than before you started Opill. You may also have some bleeding or spotting between periods.
  - Results: comprehension [94%, 95% CI (93%, 97%)]
- Statement: Opill is safe and effective for breastfeeding women
  - Results: comprehension [96%, 95% CI (94%, 98%)].
- Statement: How effective is Opill? As with any birth control methods, Opill does not prevent pregnancy all the time
  - Results: comprehension [92%, 95% CI (90%, 95%)].

Comprehension of the important CIL statement "Opill is not an emergency contraceptive" did not score well, as was the case with the DFL LCS [85%, 95% CI (82%, 88%)]. This is concerning given that hormonal emergency contraception is available as a nonprescription product, which could result in confusion.

There were also two statements in the tested CIL (as well as the currently proposed CIL) that do not appear on the DFL due to space limitations and are key aspects of usage. Therefore, it is particularly important that they be well understood because they are not reinforced elsewhere. However, neither scored well in the CIL LCS:

- Statement: If you are switching from another birth control pill, vaginal ring, or patch, start taking Opill the day after you stop the other method
  - Results: comprehension [81%, 95% CI (78%, 84%)].An analysis of the incorrect verbatims revealed that those participants typically cited "two days" or "five days" as the transition time period, thereby confusing it with other directions on the CIL.
- Statement: What if I have taken an emergency contraceptive before starting Opill? Also, use a condom (or another barrier method) every time you have sex until your next period
  - Results: comprehension [80%, 95% CI (77%, 84%)].
  - (Note: the Applicant did not formally assess this as a study endpoint; however, it was a question in the data collection instrument and the resulting data were elicited.)

These questions were asked because it is important that consumers understand how to transition between birth control products as this is likely to be a common occurrence and incorrect understanding of how to switch between products could result in unintended pregnancy.

In addition, placement and the wording of some (but not all) key messages in the previously tested version were revised in the currently proposed CIL; furthermore, the design and illustrations of the CIL have changed. All of these factors combine to suggest that the comprehension scores discussed in this review may be of somewhat limited utility in assessing comprehension of the most current version of the CIL under discussion.

Assessment of Important Subgroups

Adolescents

There were no substantial differences in comprehension between adolescent and adult participants in understanding the CIL. The same issues that were identified in the larger population with the CIL were identified in these subpopulations.

Limited Literacy

The following issues were identified when evaluating the LCS results by literacy level:

- Statement: To start using Opill: If you are switching from another birth control pill, vaginal ring, or patch, start taking Opill the day after you stop the other method.
  - Results: comprehension for normal literacy 86%, limited literacy 66%
- Statement: What if I have taken an emergency contraceptive before starting Opill?... Also use a condom (or another barrier method) every time you have sex until your next period.
  - Results: comprehension for normal literacy 87%, limited literacy 63%
- Statement: Opill is not an emergency contraceptive.
  - Results: comprehension for normal literacy 89%, limited literacy 74%
- Statement: What changes to my menstrual period are NOT expected when using Opill? Talk to a doctor while continuing to take this product every day even if you experience any of the following: you repeatedly have bleeding that is brought on by sex.
  - Results: comprehension for normal literacy 87%, limited literacy 71%

These results suggest that consumers with limited literacy may not be able to identify that norgestrel is not an emergency contraceptive product and raises concern about whether they will be able to correctly switch from a prescription contraceptive product.

3.2.2.3 Targeted Breast Cancer Self-Selection Study

Overview

At the request of the FDA, the Applicant conducted the pivotal TBCSS to evaluate whether women with a history of breast cancer could correctly determine—using only the DFL—that norgestrel tablet was not appropriate for them to use.

Two-hundred-six participants who responded yes to the question of history of breast cancer, underwent the self-selection interview. Self-selection participants were asked by the interviewer the following question, among others: “Given what you have read on the label and your own health history, is this product okay or not okay for you personally to use?.”

Both the Applicant’s and FDA’s analyses showed the lower bound of correct deselection among participants with a history of or current breast cancer approximated or exceeded the 90% threshold, indicating high rates of correct deselection. However, only 5% of the study participants were of limited literacy, a substantially inadequate representation. Therefore, the study results may be a considerable overestimation of comprehension for the general population of nonprescription users, which has a limited literary prevalence of approximately 30%.

Study Design

The objective of the TBCSS was to evaluate the adequacy of the proposed nonprescription Drug Facts Label (DFL) to assess the ability of women with a history of breast cancer to correctly determine norgestrel tablet is not appropriate for their use (correctly deselect). Participants in the self-selection

cohort were asked the following self-selection question: “Given what you have read on the label and your own health history, is this product okay or not for you to personally use?”

The primary endpoint was the proportion of participants with a history of breast cancer who did not select the product for their own use (i.e., correct deselection). The pre-specified target threshold was 90% for the LB of the 95% CI of the correct deselection.

The sample size was determined by precision of the estimate. Assuming a 95% correct response rate, a sample of 200 participants with a history of breast cancer was expected to have a 95% CI with a width of approximately ±3%. A 25% rate of limited literacy would yield 50 participants with a history of breast cancer and limited literacy, which was expected to have a 95% CI with a width of approximately ±6%.

The self-selection population was defined as all participants who confirmed a history of breast cancer, made a self-selection decision, and provided responses to all relevant medical history questions.

A qualitative review was conducted of all verbatims to independently assess participant responses as they pertained to both the endpoint and additional issues for sensitivity analyses.

Demographics

There were 206 participants included in the self-selection population. The average age was 44.2 years (standard deviation 4.7, range 31 to 50 years). Among the self-selection population, 109 (53%) were in the age group 25-45 years and 97 (47%) were women aged 46+ years. No participants were under age 24. The majority of the self-selection population self-identified as white (276 or 79%). Thirty-five participants self-identified (17%) as black/African American, and 23 (11%) self-identified as being Hispanic or Latina.

Most participants had a history of using hormonal birth control (HBC) (188 or 91%) which included 166 (81%) with a history of HBC and oral contraceptive (OC) use and 22 (11%) with a history of HBC use but no OC use. Only 10 (5%) participants were of limited literacy, which was far below the expected sample size for this subgroup.

Among the 206 participants in the self-selection population, 32 (16%) reported currently having cancer or receiving treatment, and 173 (84%) reported being in remission. There were 11 participants who currently use hormone-containing birth control, and 5 participants who had used a hormone-containing birth control since being diagnosed with breast cancer, but who no longer used it.

Study Results

The Applicant-reported correct deselection endpoint was 199/205= 97% [95% CI (94%, 99%)] (Table 4). Six (6) of 205 participants incorrectly said that it would be okay for them personally to use norgestrel tablet. The six who incorrectly responded were all of normal literacy. These six participants’ initial diagnoses had been anywhere from one month to 18 years ago. Four of six self-reported being in remission. None indicated any awareness of any DFL statements that would preclude them from using norgestrel.

Table 4. Targeted Breast Cancer Study: Applicant’s Self-Selection Table

Targeted Breast Cancer Self-Selection Population N=206	Appropriate to Use N=1	Not appropriate to Use N=205
Selector/Potential Selector (N=7)	Cell A N=1	Cell B N=6
Non-Selector (N=199)	Cell C N=0	Cell D N=199

Source: Table 9 of Applicant’s Study Report
Source: Table 10 of the Applicant’s Study Report.
Abbreviations: IUD, intrauterine device; NL, normal literacy

FDA Analysis

- One other participant (subject ID: (b) (6)) was mitigated by the Applicant in a physician review panel majority vote [5] from "inappropriate to use" to "appropriate to use" since she reported that she had been told that she could take hormonal birth control.
  - The FDA clinical reviewers do not agree with the Applicant's determination to mitigate this participant as "appropriate to use." Regardless of whether she has been previously personally told that she can take hormonal birth control, she should be under a doctor's care, not purchasing a product for nonprescription use if she has an absolute contraindication. In this particular study, the consumer decided on her own that her doctor's previous advice would apply in this case and chose to override the label. Therefore, we moved this participant from "appropriate to use" to "not appropriate to use"
- Four participants (subject IDs: (b) (6), (b) (6), (b) (6), (b) (6)) were categorized by the Applicant as non-selectors who stated that they would need to ask a doctor. FDA reviewers categorized them as selectors (they believed it was appropriate to use).

Rationale: The DFL clearly states "Do not use", rather than "Ask a doctor." There is a compelling reason why there is a "Do not use" warning on this DFL for consumers with breast cancer and survivors. If consumers do not interpret the DNU as an automatic "no" (i.e., do not use under any circumstances), there is the risk is that if a consumer is without easy access to a physician, they may interpret DNU as something they can override on their own until they are able to access a medical consultation. As a result, we moved these four participants from cell D to cell B.

Therefore, the FDA review team's correct deselection endpoint was calculated as 195/206 [95%, 95% CI (91%, 97%)] (Table 5).

Table 5. Targeted Breast Cancer Study: FDA's Self-Selection Table

Targeted Breast Cancer Self-Selection Population N=206	Appropriate to Use N=0	Not appropriate to Use N=206
Selector/Potential Selector (N=11)	Cell A N=0	Cell B N=11
Non-Selector (N=195)	Cell C N=0	Cell D N=195

Source: FDA reviewer's analysis

FDA Sensitivity Analyses

- Four participants made a correct selection for the wrong reason or a reason unrelated to their breast cancer. In this sensitivity analysis, we conservatively assumed that correct study responses needed to articulate a correct understanding of the primary reason that participants should not use norgestrel. The revised correct deselection was 191/206 [93%, 95% CI (88%, 96%)].
- 12 individuals participated who cannot bear children—these women should not have been in the study as this would not reflect a "real world" situation, and so were removed in FDA analyses
- Table 6 shows the results with both of the two modifications in the bullets above (increasing the number of "selectors" from 11 to 15, and reducing the study N from 206 to 194); this results in appropriate deselection in 179/194 [92%, 95% CI (88%, 96%).

[5] One of the Applicant's three physician reviewers who was part of the mitigation panel dissented, stating that they would need to know more about her oncological history since they didn't know the details of her cancer.

Table 6. Targeted Breast Cancer Study: FDA's Self-Selection Table for Sensitivity Analyses

Targeted Breast Cancer Self-Selection Population excluding participants unable to bear children N=194	Appropriate to Use N=0	Not appropriate to Use N=194
Selector/Potential Selector (N=15)	Cell A N=0	Cell B N=15
Non-Selector (N=179)	Cell C N=0	Cell D N=179

Source: FDA reviewer's analysis

Conclusion

The results of this study appear to indicate that most females with current or previous breast cancer would appropriately deselect from taking norgestrel tablet. However, the results also show that there are some females with current or previous breast cancer who would—in the absence of a healthcare intermediary—incorrectly consider it "appropriate to use" for themselves. The extent of this potential issue and the resulting implications in the general nonprescription setting are difficult to estimate from this study because: (1) they were not presented with the option of actually being able to use norgestrel tablet, and (2) there was a very limited number of limited literacy participants and, as such, there are real concerns as to the generalizability of the findings of this study to a real world setting.

3.2.2.4 Self-Selection Phase of ACCESS

Overview

The Applicant's actual use study - "Adherence with Continuous-dose Oral Contraceptive: Evaluation of Self-Selection and Use (or ACCESS study) - included two phases: a self-selection component (referred to as ACCESS self-selection phase or ACCESS-SSP) and the use phase (referred to as ACCESS use phase or ACCESS-UP).

The primary endpoint of ACCESS-SSP, as advised by FDA, was the assessment of correct deselection (that is: (a) whether a consumer can correctly assess that they should not use norgestrel under any circumstances or (b) whether they need to ask a doctor first, if they have a medical condition of concern. ACCESS only had a 13% limited literacy representation,[6] despite FDA advising the Applicant at several meetings during the development process to have a more robust limited literacy participation in the study

Design and Conduct of ACCESS-Self Selection Phase

The objective of the self-selection component of the AUS was to evaluate the adequacy of the proposed nonprescription labeling to guide appropriate consumer selection. The self-selection component was conducted at the beginning of each potential AUS participant's enrollment interview. The AUS was conducted from September 2019 to August 2021.

Participants were given the opportunity to read the DFL, and then were asked the questions below.

[6] Most of the ACCESS participants were enrolled in person prior to the pandemic; however, during the pandemic 161 participants (all adolescents) were enrolled remotely (92 proceeded to the use phase). Although these participants were able to use any device for the enrollment interview in order to view the DFL and other relevant materials, the REALM interview was conducted solely over the telephone. That also differs from the methodology utilized in the published validation study; the Applicant did not provide documentation to support the validity of this REALM test. Therefore, it is unclear as to the extent of validity of the Applicant's REALM results.

Self-Selection Questions

- S4: Q1: Given what you have read on the label and your own health history, is this product okay or not okay for you personally to use?
  - S4: Q1a: (If yes) Please tell me why you decided this medication is right for you to use if you were interested?
  - S4: Q1b: (If no) Please tell me why you decided this medication is not right for you take home today and start to use.
  - S4: Q1c: (If would talk to a doctor OR would talk to a pharmacist) Why would you want to talk to a doctor or pharmacist?
  - S4: Q1d (If don't know): Can you tell me why you are uncertain?

Purchase Questions

- S4: Q2 (if the answer to S4Q1 is yes):
  - For Pharmacy sites: Would you like to purchase Opill today to take home for your own use? It costs $10.00 for a 1-month supply or $20.00 for a 3-month supply.
  - For Clinic sites (for adolescents): Would you like to take this home today for your own use?
  - For remote enrollment site (implemented during the pandemic): Would you like to have this product shipped to you for your own use?
  - S4: Q2a (if the answer to S4Q2 is no): Please explain why not.
  - S4: Q2b (if the answer to S4Q2 is don't know) Pharmacy: can you please explain why you are unsure if you would like to purchase Opill? Clinic: can you please explain why you are unsure if you would like to take Opill home to use?

FDA Methods and Analysis

The FDA review team independently examined the medical histories for participants with cancer, unexplained vaginal bleeding, and liver disease. The review team did not concur with some of the Applicant's determinations of "appropriate to use."

Furthermore, FDA reviewers disagreed with the Applicant's classifications based on purchase intent. For instance, if the individual met an absolute contraindication criteria (cancer) such that they should have deselected yet responded to Q1 as "yes", but then responded no to Q2 (not to purchase), they were categorized by the Applicant as appropriate deselection. However, the categorization should have only been based upon their response to Q1 since the decision to purchase may be influenced by factors other than personal health history. Purchase decision data are not a reliable surrogate for self-selection. Moreover, the ACCESS study design did not incorporate a pathway for participants to leave the site prior to making a selection decision, in order to follow the label and ask their doctor about whether to use and then return to the study. FDA also determined that the study was not designed to elicit precise data on whether participants, after making a purchase, actually asked their doctor prior to actually starting to use norgestrel.

The detailed explanation of the reasons for the substantial difference between Applicant and reviewer results is summarized in the FDA Methods and Analysis Section and detailed in Section 5.13.

Study Demographics

ACCESS included the following overall demographic distribution: 60% self-reported whites, 30% self-reported blacks, and 6% self-reported Asians in the self-selection population; 17% were Hispanic. Females ages 11 to 14 comprised 5% of the self-selection population, and females ages 15 to 17

comprised 16% of the population. Seven males participated in the study. There were 65% participants with a previous history of oral contraceptive use. Only 13% of participants were of limited literacy. Study participants were generally healthy and reported that they were interested in using an oral contraceptive product. See Table 18 in Section 5.13.1 for additional information.

Study Results

- Correct Deselection – FDA primary endpoint: FDA analysis found that among the 92 participants who should have deselected only 25 did so (This means that correct deselection was: 27% with 95% CI (18%, 37%). The Applicant reported that out of 78 participants who should have correctly deselected, only 66 did so (This means that the Applicant's correct deselection was 85% with 95% CI (75%, 92%). Note that at 75% LB, the Applicant's endpoint was already substantially below the target threshold of 90%.
- Correct Selection – FDA secondary endpoint: FDA analysis found that overall among the total number of participants in the self-selection population, 1508 correctly selected (including those appropriate to use and those not appropriate to use). This means the correct selection (A+B)/(A+B+C+D) was 1508/1772 or 85%, with 95% CI (83%, 87%), which approaches the typical correct selection target threshold of 85% The Applicant reported that overall correct selection (A+B)/(A+B+D) was 99% with 95% CI (98%, 100%).

Table 7. ACCESS Self-Selection Results: Reviewers' Analysis

Self-Selection Population N=1772	Appropriate or Acceptable to Use N=1680	Not Appropriate to Use N=92
Selector (N=1550)	Cell A N=1483	Cell B N=67
Non-Selector (N=222)	Cell C N=197	Cell D N=25

Source: Reviewers' analysis.
Correct deselection D/(B+D): 25/92 = 27.2% with 95% CI (18.4%, 37.4%)
Overall correct selection (A+D)/(A+B+C+D): 1508/1772 = 85.1% with 95% CI (83.4%, 86.7%).
Abbreviation: ACCESS, Adherence with Continuous-dose Oral Contraceptive: Evaluation of Self-Selection and Use

Summary of Subgroup Analyses for those Participants with Absolute and Relative Contraindications (Cancer, Undiagnosed Vaginal Bleeding, and Liver disease)

Analysis of the cancer, undiagnosed vaginal bleeding, and liver disease subgroups reveals consumers failed to correctly deselect.

Cancer: [7] Three (of the eleven participants with cancer who said norgestrel was appropriate for them to use) had a potentially progestin-sensitive cancer – one with melanoma and two with breast cancer. Two of these participants (one with breast cancer, of limited literacy, and one with metastatic melanoma, of normal literacy) tried to purchase norgestrel and had to be excluded from the Use Phase as that was an exclusion criterion.

Unexplained vaginal bleeding at study enrollment: At the enrollment interview, 25 participants expressed that they had unexplained vaginal bleeding and that they had not spoken with a doctor about it: 17/25 (68%) failed to correctly deselect. Only 5 participants stated that they would want to ask their doctor before making their selection decision.

Of note, the FDA review believes study participants' ability to recognize undiagnosed abnormal vaginal bleeding has not been adequately assessed. The DFL and subsequent consumer behavior studies are

[7] Participant (b) (6) reported a history of cervical dysplasia, which is not a contraindication to norgestrel use.

based on the Applicant's underlying assumption that only intermenstrual bleeding necessitates consultation with a HCP prior to initiating norgestrel tablet use. The FDA review team disagrees with the Applicant's assertion and believes that intramenstrual bleeding that is unusually heavy or lasts longer than 8 days should also have been included in this assessment.

Liver disease: Seven participants who stated they had liver disease said that norgestrel tablets were appropriate to use. FDA Reviewers determined that 4 of these 7 were not appropriate to use. See Section 5.13 for detailed tables depicting FDA and Applicant classifications of participants in the three subgroups.

Adolescents

One adolescent, age 15, was in the cancer subgroup. She appropriately deselected. There were 5 adolescents with unexplained vaginal bleeding, and four out of these five adolescents failed to correctly deselect. No adolescents were in the liver disease subgroup.

There were insufficient data to conduct a comprehensive analysis of how many adolescent participants intended to use norgestrel tablet either solely or partially for off-label use, such as regulating periods. The reviewers assessed the verbatim responses of 26 participants at the initial self-selection interview and another 24 during the actual use portion. Of the 50 study participants who indicated off label use of norgestrel tablet, 27 (54%) were adolescents who stated they were using norgestrel tablet for reasons other than prevention of pregnancy. Given that data were not collected upon enrollment in the Use Phase as to the reason an individual participant was seeking this product, it is not possible to make a broader conclusion on whether participants, especially adolescents, understood norgestrel tablet is not indicated to treat irregular menses (very common in adolescents) or mitigate menstrual irregularities secondary to medical conditions, such as polycystic ovarian syndrome (PCOS) or thyroid disorders.

Limited Literacy Among Combined Subgroups of Interest

For all three subgroups with contraindications to use (cancer, unexplained vaginal bleeding, and liver disease) combined, there were seven limited literacy participants out of a total of 45 unique participants (one participant had both liver disease and unexplained vaginal bleeding). This proportion (7 of 45, or 16%) approximated the limited literacy proportion of 13% in the overall study population.

In the subgroup of participants with cancer, two of three limited literacy participants failed to correctly deselect, including one participant with breast cancer. In the subgroup with unexplained vaginal bleeding, three of four of limited literacy participants failed to correctly deselect. The subgroup with liver disease had no limited literacy participants.

The details on the limited literacy analysis for overall self-selection population is shown in Table 24 in Section 5.13.

Conclusion

The LB threshold of 83% for the correct self-selection endpoint, which indicated the proportion of potential users who would likely make a correct selection decision, approximates the typical 85% threshold for this endpoint. Nevertheless, the critical issue for this product is the substantial failure to correctly deselect by those for whom it is inappropriate to use norgestrel tablet, given the serious medical issues that can arise if contraindications are not followed. A second issue is there was an insufficient proportion of limited literacy participants, leaving open the potential that correct deselection rate would be even lower in the general consumer population.

The failure of those with cancer to correctly deselect is particularly concerning because the DFL used in the ACCESS study (DFL Version F) stated, "do not use if you ever had any cancer." While the current DFL

(DFL Version H) restrict the "do not use" more specifically to those with breast cancer, it is nonetheless of concern that many participants with cancer either did not see or ignored a "do not use" warning on the ACCESS DFL. In the ACCESS-SSP, three participants with potentially progestin-sensitive cancer, including two with breast cancer, failed to correctly deselect. Although the TBCSS achieved the prespecified success threshold utilizing the current DFL, it was 1) a more hypothetical exercise than the ACCESS study; 2) still had participants with breast cancer who selected to use norgestrel tablet, and 3) was likely biased upward due to only 5% limited literacy representation. Therefore, the TBCSS study findings indicate consumers with breast cancer will choose to use norgestrel tablet, but the full extent to which consumers with breast cancer in a nonprescription setting will select to use norgestrel tablet is not well-characterized.

Regarding undiagnosed abnormal vaginal bleeding, more than half of those with this condition did not correctly deselect, with some proceeding to purchase and use norgestrel tablet. Therefore, based on the study findings, together with the lack of data as to whether participants in the study actually asked a doctor before use, the FDA review team is unable to conclude that consumers with this condition can appropriately deselect.

3.2.2.5 Use Phase of ACCESS

3.2.2.5.1 Adherence to Continuous-Dose Oral Contraceptive: Evaluation of Self-Selection and Use (ACCESS)

We ask the AC to consider whether the improbable dosing may reflect a lack of understanding of the directions for use and poor adherence to correct use in a nonprescription setting.

Study Design

This was a multicenter, 24-week, open-label self-selection and actual use study. All participants who attended the initial enrollment visit were asked to make a self-selection and purchase decision in the Self-Selection Phase including participants who were male. Participants presenting with any exclusion criteria, including males, were not allowed to purchase and continue to the Use Phase of the study. Participants who chose to take the product home, used the product on their own with the assistance of the nonprescription labeling, which included the DFL, CIL, and reminder card.

Study Sites

There were 36 sites which included 25 retail pharmacy sites; ten women's health or adolescent clinic sites; and a single decentralized site used for remote enrollment. All study sites were in the United States.

Inclusion and Exclusion Criteria

Inclusion criteria included female participants 11 years of age or older. Potential participants were excluded for the following: premenarchal females, pregnancy (based on self-report or enrollment pregnancy test), history of any cancer, males, and known allergy to norgestrel or inactive ingredients.

Procedures and Schedule

For the actual use phase of ACCESS, participants were asked if they would like to purchase the product for use. This was followed by collection of medical history, demographic information, and administration of the REALM (measure of literacy). Participants took a urine-based pregnancy test prior to start of the study. Participants who said that they would like to purchase the product and did not meet any of the exclusion criteria as determined by the medical history and urine-based pregnancy test were allowed to continue to the Use Phase.

Study Drug (norgestrel tablet): The study drug cost $10 for one 28-day package or $20 for three packages. Participants were allowed to purchase up to eight 4-week supply packages during the study period (up to eight packages at a single visit but could not exceed more than eight packages in the study). Participants were not informed of the limit unless they tried to purchase more than a total of eight packages during the study. Participants recorded their use of the product using an online medication use e-diary.

E-Diary: The e-diary application was installed and set-up for use at the enrollment visit for study participants who had access to a smartphone. The Applicant provided a device for study participants who did not have access to a smartphone or tablet with internet connectivity. The following procedures regarding e-diary entry were conducted:

- The e-diary data entry form for a specific study day became visible to participants on the next day.
- Participants were asked to indicate whether they took the study product.
  - If yes, they were asked what time the dose was taken, and if they took another tablet. Participants were asked if they took an additional tablet up to four times.
  - If no, the participant was asked why they did not take the study drug on that particular day and provided the following answer choices: forgot; didn't have pills with me; ran out of pills-but plan to continue; have decided to discontinue the pill; and other reason.
  - If the participant indicated that she decided to discontinue the study drug, a reason for why she decided to discontinue was asked.
  - Participants ≥18 years of age were also asked whether they engaged in sexual activity (vaginal intercourse) and if yes, whether they used any other form of contraception to prevent pregnancy. If the participant indicated that they used another form of contraception aside from the study drug, the participant was asked to indicate what that form of contraception was.

E-diary reminders: All participants received a reminder to complete their e-diary every four days regardless of whether they had entered data on the previous days.

Telephone interviews: Scheduled contact was via seven telephone interviews conducted by trained nurse interviewers at weeks 2, 4, 8, 12, 16, 20 and 24. Interviews were scripted with the intention to gather information on if, how, and when the participant took the product; any AEs; concomitant medications; and actions the participant may have taken related to the use of the product. The data entered originally in the e-diary were the source of data used for primary and secondary adherence endpoint calculations. Participants were asked to take a self-administered urine-based home pregnancy test and record results in the electronic diary at the end of the study.

Statistical Method and Analysis

Sample size calculation was based on the precision of a single endpoint. Assuming there were 900 purchasers, if 80% of those use the product, that would yield an actual User Population of 720. Assuming an ≥ 85% correct behavior to any individual endpoints, a sample of 720 participants would have a 95% CI with a width of ±2.8%. Two-sided 95% confidence intervals CI were computed using an exact method (Clopper-Pearson).

The Purchaser Population was defined as all participants who met Use Phase enrollment criteria, signed informed consent, and purchased/obtained the study drug. The User Population, a subset of the Purchaser Population, was defined as all participants who reported use of the study drug in the e-diary.

Study Endpoints

- For an actual use study, multiple primary endpoints are used to ensure that key safety and efficacy messages are understood. These messages are derived from the prescription label and selected in order of their listing on the product. For these studies, multiple endpoints are chosen with targeted thresholds that, when achieved, represent comprehension by the participants. Below is a list of primary endpoints in the ACCESS study with predefined target thresholds. Active use study days are defined as any day on or in between a participant's first reported use and last reported use of the study drug in the e-diary.
  - Primary Endpoint A: Self-selection: Proportion of self-selection population who make a correct selection decision regarding use of the product: Target Threshold 85% lower bound (LB). The findings of this self-selection endpoint are discussed in Section 3.2.2.4 and will not be further discussed in this section on the actual use phase of ACCESS.
  - Primary Endpoint B: Actual use: Proportion of active use study days where a participant reported taking the study drug in the e-diary (dosing day analysis): Target Threshold 85% LB.
  - Primary Endpoint C: Actual Use: Proportion of participants who reported taking the study drug on 85% or more active use study days (participant-level analysis): Target Threshold 85% LB.
  - Primary Endpoint D: Actual Use: Proportion of doses reported to have been taken within 27 hours of the time of the previous dose: Target Threshold 80% LB.
- There was a total of 16 additional secondary endpoints in the ACCESS study that covered other important safety messages. Refer to Section 5.14.2 for a discussion of Secondary Endpoints F (use without another hormonal contraceptive), G (use of a condom or abstaining from intercourse when initiating therapy), J (seeking healthcare for abdominal pain), and L (seeking healthcare for heavy periods). The remaining secondary endpoints are listed in Table 29 and Table 30 in Section 5.14.1.

Summary of Issues with Study Design

- Data entry in the e-diary was retrospective and is vulnerable to recall bias
  - The e-diary data entry form for a specific study day became visible to participants on the next day.
  - Participants were allowed to enter a previous days' dosing behavior for up to ten (10) days following the dosing day.
- Participants prompted to enter data in a manner that increased likelihood of overreporting use
  - If a participant did not open their e-diary and enter data for any of the previous days, the participant was prompted to begin entering data at the earliest available incomplete date and complete the diary for each day until they reached the entry for the current day.
  - Participants were asked if they took an additional tablet up to four times.
- Participants were paid for each day they completed their diary, regardless of whether they reported taking the study drug or not. This compensation structure may have influenced the entering of information daily, even if the information recorded was not accurate.
- Sexual history not obtained in participants < 18 years old making it unclear how many of the adolescent participants were at risk for pregnancy and how many performed correct mitigating behaviors such as abstinence or use of barrier contraception when engaging in sexual activity when either initiating use of the study drug or missing a tablet
- Timing of and content of discussions between study participants and HCPs not consistently captured across study. This limits the interpretation of whether participants discussed medical conditions that

occurred before and during the study in a timely manner and whether there was adherence to critical safety messages on the proposed DFL.

Results

Study Population

A total of 955 participants purchased the product and entered the Use Phase. A total of 883 participants documented use of the product in the e-diary and constituted the User Population. Of the 883 participants in the User Population, 53% (470/883) completed 6 months of use and completed the end of study (EOS) interview, 47% (413/883) discontinued study participation (i.e., withdrew from the study or were lost to follow-up). Of the participants in the User Population, 21% (188/883) withdrew from the study, and 26% (225/883) were lost to follow-up. There were 45 participants (5% (45/883)) who withdrew due to an adverse event. Participants who withdrew from the study were asked to complete the EOS interview. Of the 883 participants in the User Population, 73% (642/883) completed the end-of-study (EOS) interview. Of the 642 participants who completed the EOS interview, 173 were participants who were withdrawn from the study. Refer to Table 28 in Section 5.14.1 for the Purchaser Population Disposition Table.

Demographics

Of the User Population, 23% (200/883) of participants were < 18 years old although most of the adolescent population was 15 years or older. There were no participants who were 11 years old in the User Population and only three participants who were 12 years old. Refer to Table 27 in Section 5.14.1 for a distribution of adolescents in the User Population by age. One notable limitation of the demographics of the analysis populations is the low proportion of participants with limited literacy. Only 14% of participants in the User Population had limited literacy, a substantial underrepresentation of the US population. Because persons with limited literacy may make a greater number of use errors, underrepresentation of this population in this study may overestimate the results on appropriate use/selection, suggesting that the results shown in ACCESS may be better than the effectiveness and safety outcomes would be with real world nonprescription use by the general consumer population.

Adherence Endpoints

The source of adherence data used to calculate the primary and secondary adherence endpoints was data entered by participants in the e-diary. The large proportion of participants with improbable dosing (discussed in detail below) is the major limitation in assessment of the endpoints that measured medication adherence and whether the participants' responses indicated correct use. As efficacy of this product requires correct use, adherence endpoints are critical to assessing whether norgestrel could be used effectively in the nonprescription setting. Below we discuss the issues related to improbable dosing prior to presenting the findings on the adherence endpoints to place these findings in proper context.

E-Diary Doses Recorded Exceeded Doses Dispensed (Improbable Dosing)

The FDA reviewers identified 261 (30%) participants for whom the total number of tablets reported as taken in the e-diary exceeded the total number of tablets dispensed to that participant during the study. The Applicant has referred to this as improbable dosing.

The Applicant provided several potential reasons for improbable dosing. These included possible human errors, such as incorrect dosing due to simple recall errors and participant misunderstanding on how to correctly report information in the e-diary. The Applicant also stated that not having feedback or a signaling mechanism from the electronic data capture that turned off the e-diary when they did not

have any more study drug as well as a lack of a mechanism that alerted and challenged the participant when they reported improbable dosing may have contributed to improbable dosing.

After FDA informed the Applicant of the dosing errors found in our analysis of the data submitted in the sNDA, the Applicant retrospectively conducted and submitted the results of a qualitative follow-up study that consisted of one-on-one interviews with 76 participants (out of the 261, or 29%) who reported improbable dosing. The objective of the study was to identify reasons these participants reported taking more doses of the study drug than dispensed. Of the 76 interviewed:

- Almost half reported inadvertently reporting excess doses in the e-diary
- Twenty-three (30%) reported having access to additional birth control that they were reporting on in the e-diary. Most of these individuals (18/23 or 78%) who reported obtaining additional birth control reported receiving more study medication packs from the study site and three participants reported receiving more study medication packs from another study participant.
- Two individuals who reported taking a birth control other than the study drug and reporting on use of this other birth control in the e-diary.

There were a number of limitations to this retrospective study, such as recall bias; the study was composed of a convenience sample; lack of a standardized format of questions asked of the interviewees. The number of limitations in the design and conduct of this study and the length of time that elapsed after the completion of the AUS present undermined the reliability of the findings from this qualitative study. This qualitative study was conducted in September 2022, meaning time duration between the time of a participant's enrollment in ACCESS to the time the qualitative study was ranged from one to three years. The FDA reviewers concluded the qualitative study did not contribute meaningful evidence to understanding the causes of improbable dosing in such a large proportion of the AUS study population.

The Applicant also submitted the results of a root cause analysis at the request of the FDA reviewers. The Applicant identified the following as major root causes:

- The absence of a design element for prevention of participant improbable dosing.
- Study design did not have a focus on identifying reported improbable dosing by study participants. This included the following:
  - Data collection and handling of data from sites and nurse interviewers as well as data collection and handling of data from participants in the e-diary were not focused on identifying improbable dosing.
  - Study plans including the monitoring plan, data management plan, and the statistical analysis plan did not have steps to identify improbable dosing.
- Issues related to the set-up of the e-diary including the following:
  - Although sites could not supply study drug after the participants' end-of-study (EOS) interview, the participant could still enter daily data including dosing data until e-diary deactivation.
  - Participants received reminders to complete the e-diary until the e-diary was deactivated.

The Applicant stated that the analysis did not indicate that over-reporting of use of the study drug was the result of a systematic issue such as issues with the e-diary, data management or operational error. The Applicant believed the over-reporting was because of inaccurate participant reporting of tablet intake. The Applicant also concluded that for the participants who over-reported to a large extent, it is most likely that this reporting was deliberate and that a financial incentive to report on dosing in the e-

diary might have incentivized participants to report having taken more doses to receive compensation for a longer period of time without having to purchase more packs of the study drug with their own funds. The Applicant reported that while no definitive conclusions could be drawn, no alternate explanation was suggested by the root-cause analysis.

Although the Applicant provided potential risk mitigation measures that might have prevented the phenomenon of improbable dosing, a definitive root cause (s) was not provided. The conclusion that participants over-reported dosing due to a financial incentive is speculative. Given the available data, whether subjects in the improbable dosing population incorrectly used the study drug or whether methods of study design incorrectly captured use of the study drug cannot be ascertained.

Improbable dosing compared to probable-dosing cohorts

The majority of participants in the improbable-dosing population cohort purchased either one or three packs during the entire study while the majority of probable-dosing participants purchased either three or six packs.

An analysis comparing the improbable-dosing cohort to the probable-dosing cohort populations indicated an overrepresentation in the improbable-dosing population regarding: self-reported race as Black or African American (44% versus 25%), a household income of less than $25,000 (39% versus 29%), limited literacy (20% versus 11%, and a high school education level or less (35% versus 23% for participants 18 years and older). There was not a differential overrepresentation of adolescent participants in the improbable dosing cohort. The fact that limited literacy was overrepresented in the improbable dose cohort raises concerns about whether this was an issue related to study conduct (such as the e-diary) or a true lack of understanding of how to correctly use the product. Further, it is also possible the probable-dosing participants could have reported taking more tablets than they did but were not classified with improbable (or inaccurate) dosing because the number of tablets reported taken did not exceed the number dispensed.

FDA is concerned the improbable dosing could reflect a misunderstanding of the directions for use for this product. Participants recorded doses that they did not take. The reasons why improbable dosing occurred are not evident, but the results reveal that the actual use of the drug was not well documented because what was documented was not possible. Because the reported dosing was not possible, it leaves us with no clarity on what one-third of study participants actually took – or if they took any drug at all. The issue of, and the magnitude of, improbable dosing also raises concerns regarding whether any of the data in the AUS can be relied upon to demonstrate appropriate use in the study population. Additional doses beyond what was actually taken may have been recorded by other study participants and just not exceeded the number of doses dispensed. The large proportion of improbable dosing raises concerns about the accuracy of reporting of the broader study population. As such, the study does not provide adequate data to properly assess patient adherence to DFL instructions.

Primary Endpoints B, C, and D in the ACCESS Study

Keeping in mind the uncertainties regarding improbable dosing in 30% of the study population, we present analyses of the primary endpoints using various assumptions. Additionally, the low proportion of participants with limited literacy in the User Population of ACCESS may not be indicative of the consumer population that will use this product and therefore, limit the generalizability of these analyses.

- Primary use endpoints (Primary Endpoints B, C, and D) in ACCESS-UP are endpoints that assess adherence to directions for taking the study drug every day and taking the study drug at the same time every day. In the primary use endpoint analyses, active use study days are defined as any day on or in between a participant's first reported use and last reported use of the study drug.

- Primary Endpoint B is a dosing-day analysis which evaluated adherence to directions to take the study drug every day The numerator for Primary Endpoint B is every active use study day on which a participant reported taking the study drug and the denominator is every active use study day on which a participant reported on their use of the study drug (and thus excluding missing e-diary days).
- Primary Endpoint C is a participant-level analysis which evaluated adherence to taking one tablet a day. The numerator included every participant who used the product on 85% or more active use study days among the days in which the participant reported on their use of the product and the denominator is the total number of participants in the User Population.
- Primary Endpoint D measured compliance with taking the tablet at approximately the same time each day (proportion of doses that were taken within ±3 hours from the time of the last reported dose). This step, in addition to taking a tablet a day, is particularly important to the contraceptive efficacy of norgestrel tablet. The numerator included: 1) all active use study days on which a tablet was taken on the day being evaluated, with time of dosing reported and 2) all active use study days on which the tablet on the day being evaluated was taken no earlier than 3 hours or no later than 3 hours after the time of day reported for the previous tablet taken. The denominator for Primary Endpoint D included all active use study days on which a dose was taken and time of dose was reported for the index day and any previous active use study day.

In Primary Endpoint D, both missing e-diary days and days reported not taking the study drug were excluded in the per-protocol analyses. The Applicant's "worst-case" sensitivity analysis imputed the missing e-diary days to not taking the study drug. However, those days reported not taking the study drug were still excluded in "worst case" analysis. Table 8 provides a summary of the endpoints, the predefined LB threshold for each of these endpoints, the type of analysis, the Applicant's result for the analysis, the FDA analysis in which participants with improbable dosing were excluded, and the FDA analysis in which participants with improbable dosing were classified as incorrect.

Table 8. ACCESS Primary Endpoints B, C, and D: Applicant's vs. FDA's Analysis

Primary Endpoint	Threshold	Analysis	Applicant's Analysis % Correct with 95% CI	FDA Analysis Excluding Participants with Improbable Dosing % Correct with 95% CI	FDA Analysis Classifying Participants with Improbable Dosing as Incorrect % Correct with 95% CI
B. Taking the IP every day	85% LB	Per protocol	93 (92, 93)	92 (92, 92)	62 (62, 62)
		Worst case	86 (86, 87)	85 (85, 86)	58 (58, 58)
C. % Participants of ≥85% adherence	85% LB	Per protocol	85 (82, 87)	83 (80, 86)	59 (55, 62)
		Worst case	72 (68, 74)	70 (66, 73)	49 (46, 53)
D. Taking the IP at the same time every day	80% LB	Per protocol	96 (96,96)	95 (95, 95)	64 (64, 64)
		Worst case	89 (89, 89)	88 (88, 88)	59 (59, 60)

Source: FDA review team, from data provided in NDA 017031 S-041.
Per Protocol: excluded missing e-diary data.
Worst case: classified missing e-diary data as a day on which the study drug was not taken
Primary Endpoint B: Use of the tablet every day (dosing-day analysis) (adherence to label message to take the product every day).
Abbreviations: CI, confidence interval; IP, investigational product; LB, lower bound

The analyses for Primary Endpoint B presented in Table 8 showed a LB ranging from 58% to 92%, based on various assumptions. Because the reasons for improbable dosing have not been well-characterized and raise concern about the accuracy of reporting of the broader study population, simply excluding

these data from this cohort is not well-supported by what we know, and FDA believes it is reasonable to also include an analysis of the data where the improbable dosing data are included and classified as incorrect use. This results in a LB ranging from 58% to 62%, which is well below the target threshold of 85% for demonstrating adherence to the labeled instructions for use.

Both the Applicant's and FDA's results of Primary Endpoint C, under various assumptions, did not meet the predesignated threshold of 85% LB (ranging from 46% to 82%). This participant-level analysis, and not the dosing-day analysis, is the most meaningful analysis in terms of understanding the likelihood of consumer adherence to daily dosing in the nonprescription setting.

All analyses for Primary Endpoint D showed a LB greater than the 80% threshold except for FDA's analyses with the improbable dosing cohort classified as incorrect use, which had a LB ranging from 59% to 64%. FDA finds this analysis reasonable to include in the range of estimates, given the aforementioned uncertainties about the reasons for improbable dosing.

FDA Additional Analyses on Taking the Product at the Same Time Each Day (Analyses D-1 and D-2)

A limitation of the Applicant's analysis of Primary Endpoint D was that the Applicant excluded all days that the participant reported not taking the product in the denominator because these days were considered as non-evaluable for time of dose. The FDA concludes the more conservative measure of adherence to dosing at the directed time needs to account for all days where the participant needed to take the study drug at the appropriate time as incorrect use, because not taking the drug each day, can lead to an unintended pregnancy.

FDA conducted additional analyses to further assess incorrect use in which all days in which participants reported on use of the study drug were included in the denominator (excluding days with missing data and start dates). This analysis is referred to as D-1. The FDA's "worst-case" analysis for D-1 imputed both missing e-diary days and days reported not taking the product as incorrect.

In addition to the D-1 analysis, FDA reviewers also conducted a separate participant-level analysis of the proportion of participants with ≥85% adherence to taking the study drug at the same time every day. This exploratory analysis will be referred to as D-2. Analysis D-1 and D-2 are displayed in Table 9.

Table 9. ACCESS Primary Endpoints D-1 and D-2 - FDA Analysis

Primary Endpoint	Threshold	Analysis	FDA Analysis Including All Participants % Correct (95% CI)	FDA Analysis Excluding Participants with Improbable Dosing % Correct (95% CI)	FDA Analysis Classifying Participants w. Improbable Dosing as Incorrect % Correct (95% CI)
D-1. Taking the IP at the same time every day	80% LB	Per protocol	89 (88, 89)	87 (87, 88)	59 (59, 59)
		Worst case	83 (82, 83)	81 (81, 82)	55 (55, 56)
D-2. % of Participants with ≥85% same time adherence	80% LB	Per protocol	74 (71, 77)	72 (68, 76)	51 (47, 54)
		Worst case	62 (59, 65)	60 (56, 64)	42 (39, 45)

Source: Created by FDA review team from data provided in NDA 017031 S-041.
Per protocol: excluded missing e-diary.
Worst case: classified missing e-diary as incorrect.
Abbreviations: CI, confidence interval; IP, investigational product; LB, lower bound

The FDA analysis of Primary Endpoint D-1 where all active use study days of participants with improbable dosing were excluded was above the threshold of 80% LB (81% to 87%) while the analysis which classified all active use study days of participants with improbable dosing as incorrect resulted in a LB well below this threshold (55% to 59%). All of the results of the FDA participant-level analyses for Primary Endpoint D-2 were below the predefined threshold for Primary Endpoint D.

Primary Endpoint Summary

- These analyses show that when dosing-day data from participants who reported improbable dosing were classified as incorrect use and days that were not reported were included as incorrect use, adherence was poor (LB as low as 55%).
- Similarly, looking at the proportion of participants with minimally acceptable adherence (at least 85%), the adherence was also poor (LB as low as 39%).
- For taking study drug at the same time every day, only omitting individuals with improbable dosing (a non-conservative assumption), leads to an adequate level of adherence. In a conservative participant-level analysis of taking the study drug at the same time every day, adherence was poor.

Secondary Endpoints B, C, and D (Taking the Tablet Every Day and at the Same Time Each Day Accounting for Mitigating Behaviors)

Secondary Endpoints B, C, and D in the ACCESS study assess adherence to directions for taking the study drug each day at approximately same time every day accounting for mitigating behaviors. A mitigating behavior was defined as using a condom (or another barrier method) for any act of intercourse or abstaining from intercourse for the following two calendar days in the event of a delayed or missed tablet. Refer to Table 29 in Section 5.14.1 for detailed summaries of the Applicant and FDA analyses of Secondary Endpoints B, C, and D which include analyses in which participants with improbable dosing were excluded and participants with improbable dosing were classified as incorrect. One major limitation of these secondary endpoint analyses in the adolescent subpopulation was that sexual history was not obtained in participants <18 years old. Assessment of consumers' ability to understand and follow the instructions for use and mitigating behaviors is important because efficacy of this product is dependent on strict adherence to the dosing regimen. The absence of these data precludes a comprehensive assessment of adherence to instructions for use and mitigating behaviors in the adolescent population.

3.2.2.5.2 ACCESS Secondary Endpoints E-O

Secondary endpoints E-O were designed to assess actions pertaining to use directions (important for efficacy of the product) and safety-related messages in the Use Phase of the ACCESS study. Limitations of assessment of some secondary endpoints include 1) small sample sizes due to the low frequency of certain medical situations and 2) lack of information on the timing of seeking the advice of a HCP in relation to some of the events. Additionally, FDA disagrees with the Applicant's methodology for assessing some of these endpoints. For example, for conditions where the DFL directs participants to "talk to a doctor" or "ask a doctor or pharmacist before use," FDA assessed the action as incorrect if the participant did not specify why they spoke to a HCP or if they spoke to a HCP about a different issue and not the medical condition of interest. In contrast, for some of the secondary endpoints, the Applicant assessed the action as correct regardless of the timing or content of the discussion with the HCP. Furthermore, the low proportion of participants with limited literacy in the User Population limits the generalizability of these results to the general consumer population. (See Section 5.14 for tables and additional discussion of ACCESS secondary endpoints.)

The following discusses endpoints related to anticipated common real-world scenarios: (1) drug interactions in general (important for safety or efficacy); (2) use of ulipristal acetate emergency contraception (important for efficacy of ulipristal); and (3) concomitant use of hormonal contraceptives (important for safety).

Drug Interactions

Secondary endpoint H assessed the proportion of participants who were taking one of the drugs listed in the "ask a doctor or pharmacist before use" (AADPBU) section of the label and completed the correct action. Due to the clinical context of the AADPBU warning and the consequences of decreased effectiveness of POCs with use of these hepatic enzyme inducers, the warning on the proposed DFL directs consumers to ask a doctor or pharmacist before use if they are currently using one of the products listed. Of the 20 participants who reported taking one of the drugs listed, two participants (10%) did not select the drug and cited the AADPBU warning as the reason they did not select to use norgestrel. An additional three subjects endorsed speaking to a HCP about the study drug. However, the timing of the discussion relative to the start of norgestrel use is unknown.

Ulipristal Acetate

Because of the expected low frequency of the event, the ACCESS study did not assess whether participants who used ulipristal acetate emergency contraception followed the correct action of waiting five days after taking ulipristal before initiating norgestrel use. Taking norgestrel earlier than the 5 days may reduce the efficacy of ulipristal to prevent a pregnancy. The study also did not assess whether participants correctly used additional nonhormonal contraception when initiating norgestrel use after use of ulipristal acetate emergency contraception. The message was tested in the CIL comprehension study as a non-primary endpoint and the comprehension rate was inadequate, given the risk of unintended pregnancy if not understood. See Section 3.3.4.4.

Concomitant Use With Other Hormonal Contraceptives

Secondary Endpoint F assessed behavior associated with the DFL warning "Do not use with other hormonal birth control products." Eleven participants reported concomitant use of a hormonal birth control product. Of these, 8 reported use of a hormonal birth control product at enrollment and three initiated use of another hormonal birth control product or IUD after enrollment. Out of the 11 participants, only three reported discontinuing the other birth control product during the study. Participants reported concomitant use of the following hormonal birth control products in the ACCESS study: Depo Provera (medroxyprogesterone acetate 150 mg), Nexplanon (etonorgestrel 68 mg implant), Mirena (levonorgestrel 52 mg) IUD, Plan B (levonorgestrel 1.5 mg), Kyleena (levonorgestrel 19.5 mg) IUD, and Junel Fe (norethindrone 1 mg and ethinyl estradiol 20 µg).

Conclusion

The above findings indicate, in a nonprescription setting, consumers may not correctly follow use directions or take correct actions in response to these important DFL messages, demonstrating either a lack of awareness or lack of comprehension of these messages, or potentially a willingness to overlook or disregard the importance of these messages.

3.3 Safety Issues

Safe use of a nonprescription product necessitates consumers correctly using the product without the assistance of a learned intermediary. It is critical that individuals using norgestrel tablet as a daily oral contraceptive understand and follow key messages pertaining to safe use of the drug:

- “do not use”;
- “ask a doctor before use” and “ask a doctor or pharmacist before use” for warnings regarding contraindications or conditions for which it may be acceptable for an individual to use the product in specific circumstances;
- “when using this product” for warnings regarding adverse events and situations that may arise during use of the product; and
- “talk to a doctor if” or “seek medical attention immediately if” for warnings regarding symptoms of conditions such as abnormal uterine bleeding that may occur during use of the product that require medical attention. Some of these symptoms, such as those of an ectopic pregnancy, may signify a condition that requires emergent medical evaluation.

Key safety issues that need further consideration include:

- What is the potential impact of consumers with a history of or current diagnosis of breast cancer using this product?
- What is the potential for concomitant use with or confusing this product with other types of hormonal birth control or emergency contraceptives?
- What is the impact of participants not understanding that they need to be evaluated by a HCP prior to use if they have unexplained bleeding, such as irregular menses? Should there be concern about consumers not having the ability to know whether the irregular bleeding is from the product or from a serious condition such as an ectopic pregnancy?

The safety profile of norgestrel tablet 0.075 mg has been established through the original clinical studies and from postmarketing data obtained during marketing (1974-2005) in the United States. The potential risk for thromboembolic events and effects on depression and mood disorders are represented in class-labeling for progestin-only contraceptives and are also relevant to Opill (though not yet described in the Opill USPI). In addition, uncertainty exists regarding the impact of chronic norgestrel use on bone mineral density, particularly in adolescents (see Section 3.3.5.1). Although these safety concerns are relevant to norgestrel tablet regardless of its prescription or nonprescription status, the FDA review team believes these important safety concerns warrant consideration by the Advisory Committee as part of the safety considerations for the potential switch to nonprescription use. Further, without a learned intermediary in the nonprescription setting, consumers with these risks may not be screened, diagnosed, or treated as optimally as in the prescription setting.

3.3.1 Sources of Data for Safety

The sources of safety data for the prescription-to-nonprescription switch of norgestrel tablet 0.075 mg discussed in this briefing document include:

- The safety data from the three interventional clinical studies to support this application (OPTION pilot AUS, ACCESS-UP, and the Delayed Pill Intake study).
- Postmarketing safety data for the marketed formulation of norgestrel and for levonorgestrel (the active component of norgestrel). Levonorgestrel data include data for the subdermal implant, the IUD, and the oral formulation. Levonorgestrel data were included because it is the levo-enantiomer of norgestrel and is responsible for its biologic activity and norgestrel tablet 0.075 mg has not been marketed as a single ingredient product since 2005.

- The safety data for both norgestrel and levonorgestrel were sourced from the following postmarketing surveillance safety databases. The time period of the reported data is indicated in parentheses:
  - Food and Drug Administration Adverse Event Reporting System (FAERS), and Spontaneous Reporting System (norgestrel and levonorgestrel: 1969-2020)
  - World Health Organization (VigiBase) (norgestrel 1978-2005) (levonorgestrel 1978-2020)
- The safety data for norgestrel only were sourced from the following databases. The time period of the reported data is indicated in parentheses:
  - American Association of Poison Control Centers (National Poison Data System)(1999-2005)
  - Data (clinical trial and postmarketing) from the original marketing Applicant (1987-2012)
- Published literature pertinent to safety and use of progestin-only contraceptives containing norgestrel or levonorgestrel.
- Structured literature-based risk assessment conducted by the Applicant:
  - Thromboembolic events targeted literature review report.
  - Bone mineral density targeted literature review report.

3.3.2 Safety Summary

The approved norgestrel prescription labeling references a total of eight US clinical studies with 2,173 women who completed at least one cycle and 648 women who completed at least 13 cycles providing a total of 21,856 28-day cycles of exposure in women aged from 15 to 49 years based on data available from the clinical studies conducted to support the original NDA.

The AUS study was an important opportunity to capture adverse events that occurred in a simulated nonprescription setting. Although adverse events are not collected using the same methodology as a phase 3 clinical trial, adverse events were collected during use of norgestrel tablet as a daily oral contraceptive (refer to Section 3.2 for a discussion of the design of AUSs). This supplemental application contains safety data from 109 participants who recorded use of the study drug in the e-diary in the OPTION pilot AUS and 883 participants in ACCESS-UP. No deaths were reported in this sNDA submission.

Extent of Exposure: ACCESS and OPTION Studies

In the ACCESS study, there were 83,348 active use study days where participants reported taking the drug in the e-diary. Excluding the active use study days of all participants with improbable dosing, there were 55,967 active use study days. ACCESS-UP was a 6-month study and over half (51.1%; 451/883) of the participants in ACCESS-UP reported taking the study drug into Study Day >140 which was the final 28-day period allowed in the study protocol.

The OPTION study was planned as a 16-week study but was terminated early, approximately 3 months after the first participant visit due to failure of the e-diary and none of the planned endpoints were analyzed. Active use days could not be calculated.

Adverse Events in ACCESS and OPTION Studies

There were four participants with four serious adverse events (SAEs) excluding pregnancy in the User Population of ACCESS-UP. The Applicant reported one SAE excluding pregnancy in the OPTION study. There was a single thromboembolic event reported in ACCESS-UP and a causal link to the study drug cannot be excluded. See Section 3.3.6.1 for a discussion of this event. The adverse events in the ACCESS and OPTION AUSs were qualitatively and quantitatively similar to the known adverse effect profile of this product.

Postmarketing Data

No new safety signals were identified in the postmarketing data evaluated from the FDA safety databases, WHO Vigibase, American Association of Poison Control Centers National Poison Data System, and the Applicant's database for this review. There were 23 cases reported for thromboembolic AEs in the WHO ex-U.S. database. However, a high rate of thromboembolic AE case reporting was not seen in any of the other postmarketing safety databases. There are many unknowns regarding the case histories involved and patterns of reporting in these cases.

FDA did not identify a definitive safety signal or trend based on the literature review submitted by the Applicant. The structured literature review on risk of venous thromboembolism did not support increased risk of venous thromboembolism with use of norgestrel and POCs. FDA notes that there is a potential safety signal of decreased accrual of bone mineral density in adolescents: 1) with Depo Provera use, which resulted in a limitation of use and 2) one study that demonstrates chronic oral progestin use in adolescents may decrease bone mineral density (BMD). It is unclear whether this safety concern can be applied to adolescents who may choose to chronically use norgestrel.

3.3.3 Preapproval Determination of Safety in the Prescription Setting

At the time of the original approval of norgestrel tablet 0.075 mg, the safety profile described in the physician labeling (now known as the United States Prescribing Information, or USPI) was primarily based on knowledge of the safety profile of combined oral contraceptives containing both a progestin and an estrogen. In 2017, the Applicant submitted labeling supplements updating the USPI to reflect current knowledge of the safety profile of norgestrel tablet 0.075 mg.

Serious adverse events plausibly attributable to Ovrette (current proposed proprietary name, Opill) did not occur in the original clinical trials. Adverse reactions occurring in > 5% of the clinical study population included: headache; dizziness; nausea; increased appetite; abdominal pain, cramps, and bloating; fatigue; vaginal discharge; dysmenorrhea; nervousness; backache; breast discomfort; and acne. Approximately half of study participants experienced bleeding pattern alterations, the most commonly reported adverse reaction and the most commonly reported reason for study product discontinuation (see Ovrette/Opill USPI (2017)).

3.3.4 Known Safety Concerns and Implications for the Nonprescription Setting

FDA notes that, overall, norgestrel and other progestin-only contraceptive products have been demonstrated to be safe in the prescription setting, where safety issues can be prevented or mitigated by assistance from HCPs. In a nonprescription setting, we ask the advisory committee to consider whether consumers will be able to interpret certain key safety messages about breast cancer and undiagnosed vaginal bleeding. In addition, there is also concern that some consumers may not consistently use the product correctly on a chronic basis and be at risk for pregnancy, but not recognize that they are pregnant because of the irregular bleeding that would be ascribed to the known side effect of norgestrel. Finally, there is a concern that consumers may not understand that this product needs to be used at the exact time every day on a daily basis to ensure prevention of pregnancy. This is unlike the majority of currently marketed prescription oral contraceptive products. Many consumers who have previously used prescription oral contraceptive products may not recognize this and fail to take norgestrel in a timely manner, potentially resulting in unintended pregnancy.

3.3.4.1 Known or Suspected Carcinoma of the Breast, or Other Progestin-Sensitive Cancer, Now or in the Past

Exogenous hormones such as norgestrel 0.075 mg may increase the likelihood of cancer recurrence in individuals with a history of a hormone-sensitive cancer. Current norgestrel tablet 0.075 mg prescribing

information contraindicates use in individuals with known or suspected breast cancer or if the patient has a diagnosis of a progestin-sensitive cancer, now or in the past.

In the nonprescription setting, consumers must be able to appropriately deselect from use of norgestrel tablet 0.075 mg if they have a history of or current breast cancer or ask a doctor before use if they have a history of other types of cancer to ensure exclusion of women that may have a progestin-sensitive cancer. The study results in the Applicant's submission raise concern that consumers will not appropriately deselect. In the DFL LCS, comprehension of "do not use if you have or ever had breast cancer [84%, 95% CI (80%, 87%)] did not meet or approximate the 90% LB threshold; moreover, among adults, comprehension was lower, at 75% LB. Although the targeted breast cancer self-selection study met the 90% threshold, the inadequate limited literacy representation of 5% in that study limits generalizability of findings. Additionally, two individuals with a history of breast cancer selected to use the product in the self-selection phase of ACCESS-AUS. One of these individuals attempted to purchase the product and had to be excluded from the study based on exclusion criteria. Another individual with metastatic melanoma also failed to correctly deselect and was excluded from purchase.

3.3.4.2 Undiagnosed Abnormal Vaginal Bleeding

Among the most important safety concerns with norgestrel tablet is the use of the product without an adequate evaluation of undiagnosed abnormal vaginal bleeding. The prescribing information contraindicates norgestrel tablet use when undiagnosed abnormal uterine bleeding, which presents as abnormal vaginal bleeding, is present at the time of treatment initiation. Although endometrial cancer occurs rarely in reproductive age women (0.037% in women under the age of 50) (Surveillance 2019), abnormal uterine bleeding accounts for approximately one-third of visits to the gynecologist. Therefore, ensuring adequate consumer comprehension and behavior is crucial for safe and effective use of this product in the nonprescription setting.

The FDA review team cannot definitively conclude that consumers with abnormal vaginal bleeding at baseline can correctly deselect from nonprescription norgestrel tablet use as a daily oral contraceptive. Consumer confusion regarding vaginal bleeding is evident throughout the consumer comprehension studies conducted by the Applicant. In addition, the DFL as tested does not differentiate for consumers the difference between abnormal uterine bleeding that may be pre-existing versus abnormal uterine bleeding that may develop during use of the product. During the ACCESS AUS, the Applicant did not collect menstrual diaries/bleeding information at baseline or throughout the study (i.e., participants reported adverse events related to bleeding only), precluding conclusions regarding appropriate behaviors in response to labeled vaginal bleeding warnings. Although the adverse event profile and discontinuation rates due to bleeding events in the ACCESS AUS were consistent with the known safety profile of norgestrel, it is unclear that consumers will be able to differentiate between bleeding that requires medical attention versus bleeding that may occur as expected due to norgestrel use.

3.3.4.3 Bleeding Pattern Alterations

Progestin-only contraceptives (POCs) frequently cause changes in menstrual bleeding patterns, resulting in irregular bleeding, spotting, and sometimes amenorrhea. The unpredictability of altered bleeding patterns causes many individuals to discontinue use of POCs. Because irregular menstrual bleeding or spotting is a common side effect of norgestrel tablet, consumers using norgestrel tablet may not seek timely care when experiencing irregular vaginal bleeding that may be secondary to uterine neoplasia, endocrine disorders (e.g., thyroid disorders), or early pregnancy. In the nonprescription setting, consumers must be able to recognize when consultation with a HCP may be necessary.

It is unclear consumers will be able to identify when the abnormal bleeding pattern requires a HCP's intervention.

3.3.4.4 Drug Interactions

Common Drug Interactions

Drug or herbal products induce certain hepatic enzymes, including CYP3A4, which in turn may decrease the effectiveness of progestin-containing oral contraceptives leading to unintended pregnancy. Examples include phenytoin, carbamazepine, barbiturates, rifampin, efavirenz, bosentan, and herbal preparations containing St. John's Wort (hypericum perforatum). If concomitant use of an interacting drug cannot be avoided, the prescribing information for norgestrel tablet 0.075 mg recommends initiating use of additional nonhormonal contraception (e.g., barrier contraception such as condoms) and continuing use for at least 28 days after discontinuation of the interacting drug. However, if use of the interacting drug is expected to be chronic (such as for long-term management of seizure disorders or HIV), then the patient and provider should consider whether an alternative contraceptive method should be used.

Of note, participants demonstrated lower than desired comprehension of the secondary endpoint pertaining to use of interacting drugs (78% [95%, (74%, 82%)]) in the DFL label comprehension study. Given the consequences of an unintended pregnancy if not well understood, for this study, FDA reviewers do not consider a point estimate of 78% a sufficiently understood endpoint.

Among the ACCESS self-selection population, 20 participants self-reported current use of one of these drugs at the time of the enrollment interview (55% continued into the Use Phase of the study). Secondary Endpoint H in the ACCESS AUS attempted to assess whether participants who reported using an interacting drug completed a correct action in response to the DFL. The DFL instructs consumers to ask a doctor or pharmacist before use of norgestrel tablet. However, the timing of this discussion (i.e., whether discussion with a doctor or pharmacist occurred before use of the drug) is unknown, limiting interpretation of this endpoint. (See Section 3.2.2.5.2 and Table 30 in the 5.14.1 for further discussion.)

Ulipristal Acetate

Emergency contraceptive ulipristal acetate effectiveness may be decreased if progestin-containing hormonal contraceptives are used within 5 days after ulipristal acetate dosing. The norgestrel prescribing information recommends initiating norgestrel tablet no sooner than 5 days after the intake of ulipristal acetate. Additional nonhormonal contraception should be used until the next menstrual period (Ovrette/Opill USPI (2017)).

In the nonprescription setting, consumers must be able to "ask a doctor or pharmacist before use." It is important for consumers to understand when to start this new oral progestin contraceptive after using ulipristal acetate for emergency contraception. Most importantly, consumers must be able to understand the consequences of failure to follow the labeled instructions, i.e., contraceptive failure and unintended pregnancy.

Similar to drug interactions, in the DFL LCS, participants demonstrated lower than desired comprehension of this secondary endpoint ("Ask a doctor or pharmacist before use if you have used an emergency contraceptive product [morning after pill] containing ulipristal acetate in the past 5 days") (82% [95% CI, 77%, 85%]). Of note, comprehension in the limited literacy and younger adolescents (ages 11-14) was lower than the total LCS-only population (PEs of 73% and 69%, respectively). (See Table 11 secondary endpoint I, Section 5.10). These data show that limited literacy consumers and younger adolescents are likely to have less of an understanding of the need to wait five days to initiate norgestrel use after taking ulipristal acetate for emergency contraception.

3.3.4.5 Acute Liver Disease

The prescription drug label contains a warning regarding norgestrel tablet use in the presence of acute liver disease. In the nonprescription setting, consumers must be able to follow the labeled instructions to "ask a doctor before use" if they "have liver problems." In the DFL LCS, there was strong understanding of "Ask a doctor before use if you have liver problems" (94%, 95% CI (91%, 96%). In ACCESS self-selection, four participants failed to correctly deselect; these results indicate that females with liver disease may not correctly deselect.

3.3.5 Uncertain Safety Concerns

3.3.5.1 Bone Mineral Density

Long-term use of progestin-only contraceptives may potentially negatively impact BMD.

Data on the impact of progestin-only contraception on BMD are most readily available for depot medroxyprogesterone acetate intramuscular injection (DMPA-IM, initial US approval 1992). Because of bone loss and lack of full recovery of this loss after treatment discontinuation, the prescription drug label of this drug has a boxed warning, recommending against use longer than 2 years unless those contraceptive methods are inadequate. Because peak bone mass accretion does not occur until approximately age 30, blunting of peak bone mass accretion with chronic DPMA use in adolescents and young adults could increase the risk of fracture later in life. Whether reduction in peak bone mass accretion increases the risk of osteoporotic fracture later in life remains unknown.

Limited data exists on the impact of progestin-only contraceptives on bone mineral density (e.g., subdermal implants, daily oral regimens). A recent study in Europe to assess the safety of a dienogest-only oral contraceptive tablet in adolescents receiving treatment for endometriosis demonstrated a decrease in lumbar BMD after 52 weeks of treatment, with partial recovery after 6 months (Ebert et al. 2017). As a 19-nortestosterone derivative, chronic norgestrel use could affect BMD similar to dienogest. Because of the signal of BMD loss and the oral progestin, there is uncertainty regarding chronic use of norgestrel tablet and effects on BMD, especially in adolescents.

3.3.6 Relevant Safety Findings From Supplemental Application

3.3.6.1 ACCESS and OPTION AUS

SAEs Reported in the ACCESS AUS

FDA review team's Safety Population (n=883), also known as the User Population, included all participants who documented use of the study drug at least once in the e-diary. Relevant SAEs are discussed below.

Pregnancy

Fourteen pregnancies occurred in ACCESS study participants; 11 of these were in the ACCESS User Population. The FDA review team classified 10 pregnancies as "exposure during pregnancy"[8] due to the timing of conception and initial intake of norgestrel. The FDA review team classified nine pregnancies as on-treatment. (FDA considers on-treatment pregnancy as pregnancy due to contraceptive failure. FDA defines on-treatment pregnancy as a pregnancy with an estimated date of conception between the date of first study product use through seven days after the last study product use ([See Section 3.1.1]). Four pregnancies were classified as pre-treatment (participant was pregnant before study product initiation),

[8] All pregnancies classified as "exposure during pregnancy" are categorized as Serious Adverse Events (SAEs) by convention. However, there are no known adverse effects in pregnancy of exposure to Norgestrel.

and one pregnancy was classified as post-treatment (estimated date of conception was more than seven days after the last study product use).

Two pregnancies occurred in females with BMI ≥ 25 kg/m^2 (i.e., overweight) and 3 occurred in females with BMI ≥ 30 kg/m^2 (i.e., obese). Four pregnancies occurred in females with normal weight. Six pregnancies occurred in participants who reported missed doses in the e-Diary at various times during the study as well as in the last 28 days of product use before the diagnosis of pregnancy. One pregnancy occurred in a participant in the improbable dosing cohort; we cannot assess the dosing pattern as it relates to the pregnancy for this participant.

Eight pregnancies were identified between 5 and 8 weeks gestational age (GA). One pregnancy was diagnosed at 12 weeks GA, and one pregnancy was diagnosed at 17 weeks GA. The gestational age at the time of diagnosis of 3 pregnancies is unknown due to loss to follow-up. Pregnancy outcomes were available for 3 participants: one full-term live birth, and 2 elective abortions. The outcomes for the remainder of the pregnancies are unknown due to loss to follow-up.

Medical SAEs:

Four participants had medical SAEs, one each of: congestive heart failure, worsening strep throat, type 1 diabetes mellitus with ketoacidosis, and eccentric mural thrombosis of the internal jugular. Although the first three are unlikely to be drug-associated, eccentric mural thrombosis is a thromboembolic event that could have a plausible association. Except for injectable medroxyprogesterone acetate, the evidence for association of thromboembolic events with POCs is not as strong as combined oral contraceptives and a warning regarding thromboembolic events does not exist on the current prescription labeling for norgestrel tablet. The participant had a family history of familial hypercholesterolemia and comorbidities that the participant's physicians believed may have contributed to this participant's AE. However, a causal link to norgestrel tablet cannot be excluded based on the available information in this case.

Discontinuation of Study Drug Due to an Adverse Event in the ACCESS AUS

In total, 64 of 883 participants (7%) discontinued study drug ACCESS-UP because of an adverse event. The most common reason for drug discontinuation was bleeding irregularities (menorrhagia, menstruation delayed, menstruation irregular, metrorrhagia, oligomenorrhea, polymenorrhea, vaginal hemorrhage) reported by 33 of these 64 participants (52%). This is consistent with what is known in the prescription setting - bleeding pattern alteration is a common reason for drug discontinuation.

Adverse Events Reported in ACCESS-UP

Overall, 341 of 883 participants (39%) in ACCESS-UP reported an adverse event. The most frequently reported adverse events were related to the reproductive system (e.g., irregular bleeding) and breast disorders.

Compared to known safety profile of norgestrel tablet and POPs, no new safety signals or trends were identified in the ACCESS adverse event safety data.

3.3.6.2 Postmarketing Databases

A postmarketing safety data review was conducted for both norgestrel and levonorgestrel products. Levonorgestrel data were included because it is the levo-enantiomer of norgestrel and is responsible for the biologic activity of norgestrel and norgestrel tablet 0.075 mg has not been marketed as a single ingredient product anywhere in the world since 2005. Levonorgestrel has been available as a single component oral product for emergency contraception and has been available as a contraceptive in the

forms of a subdermal implantable device and an IUD since the 1990s. Levonorgestrel has been available as a nonprescription oral tablet for emergency contraception since 2006.

The Applicant also provided a separate presentation of all thromboembolic AEs for each postmarketing safety database report in the sNDA. This presentation was undertaken by the Applicant after a high number of cases was observed by the Applicant for thromboembolic AEs for norgestrel in the external U.S. WHO data (23 thromboembolic AE cases ÷ 100 total cases). Further information especially regarding comorbidities that raise the risk of thromboembolic adverse events was not available. The other postmarketing safety databases did not have a similar number of cases reported for thromboembolic events for norgestrel. The Applicant also conducted a targeted literature review to assess the evidence for increased risk of thromboembolism when norgestrel was used as a daily oral contraceptive. The Applicant concludes that the evidence does not suggest that use of oral norgestrel 0.075 mg when used daily results in a clinically concerning increase in the risk of thromboembolism and the FDA reviewers agree with this conclusion.

No additional new safety concerns were identified based on the known safety profile of norgestrel tablet.

3.4 Safety in Adolescents

Adolescents represent a population of special concern with regard to the nonprescription availability of norgestrel. However, insufficient data preclude conclusions regarding use in adolescents due to small sample size, inadequate representation of younger adolescents (i.e., adolescents ages 11-15), and lack of data on sexual history and sexual activity.

Although there were 49 participants <15 years old in the User Population of ACCESS-UP, there were no participants that were 11 years old and only three that were 12 years old. Based on the ACCESS study, generalizability of use to consumers <12 years old cannot be established. The breakdown by age in the adolescent population of ACCESS is shown in Table 27.

The Applicant did not collect information on sexual history at enrollment, nor elicit sexual activity during study participation in the adolescent population. As a result, the FDA review team cannot confirm that the study was conducted in adolescents who were sexually active during the study. Since questions regarding sexual activity were not asked, it is unclear how many of the adolescent participants were at risk for pregnancy. It is also unclear how many adolescent participants performed correct mitigating behaviors such as abstinence or use of barrier contraception when engaging in sexual activity when either initiating use of this product or missing a tablet.

As previously discussed, younger adolescents in particular demonstrated low comprehension of certain key labeling messages such as the need for additional nonhormonal contraception (e.g., condoms) when first starting the drug or after missing a dose; and starting the next pack the day after finishing the last one. Moreover, this age group also scored low in comprehension of “Do not use as an emergency contraceptive.” In addition, adolescents, primarily with normal literacy, represented a significant proportion of study participants who reported "off-label” use of the norgestrel study drug product in ACCESS-UP (20/24, 83%), raising concerns that many adolescents used the norgestrel study drug product for a purpose other than its approved indication. Fourteen (14/24, 58%) individuals in the 11- to 14-year-old age group endorsed “off-label” use of norgestrel primarily to help with symptoms associated with their menstrual cycle or regulation of their menstrual cycle.

The impact of chronic use of the proposed norgestrel product on bone health in adolescents remains unclear. As discussed in Section 3.3.5.1, no direct experience exists with chronic norgestrel use and its effects on bone mineral density. Postmarketing experience for norgestrel from original approval in 1973 until 2005 does not reveal a potential concern for high fracture risk in the general population that used

this product. However, norgestrel tablet 0.075 mg has not been marketed since 2005 and is not currently marketed anywhere in the world. It is unclear how many adolescents used this product during the time it was available. A lack of available data limits our ability to assess the impact of chronic use of the proposed norgestrel product on bone mineral density in the adolescent population.

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Guidance for Industry: Label Comprehension Studies for Nonprescription Drug Products (August 2010)

Draft Guidance for Industry: Establishing Effectiveness and Safety for Hormonal Drug Products Intended to Prevent Pregnancy (July 2019)

5 Appendix

5.1 Current Prescription and Patient Labeling for NDA 017031

Opill® Tablets

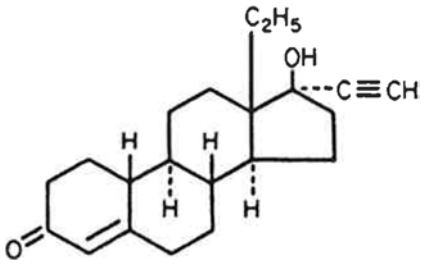
(norgestrel tablets)

Rxonly

Patients should be counseled that oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases (STDs) such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

DESCRIPTION

Each Opill tablet contains 0.075 mg of a single active steroid ingredient, norgestrel, a totally synthetic progestogen. Norgestrel is designated as (□)-13-Ethyl-17-hydroxy-18,19-dinor-17a-pregn-4-en-20-yn-3-one and is included in the formulation as a racemate. The inactive ingredients present are cellulose, FD&C Yellow 5, lactose, magnesium stearate, and polacrilin potassium.



Norgestrel

$C_{21}H_{28}O_2$ M.W. 312.45

CLINICAL PHARMACOLOGY

1. Mode of Action

Progestin-only oral contraceptives such as Opill Tablets prevent conception by suppressing ovulation in approximately half of the cycles in users, thickening the cervical mucus to inhibit sperm penetration, lowering the midcycle luteinizing hormone and follicle-stimulating hormone peaks, slowing the movement of the ovum through the fallopian tubes, and altering the endometrium.

2. Pharmacokinetics

Serum progestin levels peak about two hours after oral administration, followed by rapid distribution and elimination. By 24 hours after drug ingestion, serum levels are near baseline, making efficacy dependent upon rigid adherence to the dosing schedule. There are large variations in serum levels among individual users. Progestin-only administration results in lower steady-state progestin levels and a shorter elimination half-life than concomitant administration with estrogens.

INDICATIONS AND USAGE

Opill Tablets are indicated for use by females of reproductive potential to prevent pregnancy.

Opill Tablets are not for use as emergency contraception.

In eight US clinical studies with Opill Tablets, 2,173 women completed at least one cycle and 648 completed at least 13 cycles providing a total of 21,856 28-day cycles of exposure in women aged from 15 to 49 years. The racial demographic was 53% Caucasian and 47% African American. The pregnancy rate was approximately 2 per 100 women-years.

CONTRAINDICATIONS

Opill Tablets is contraindicated for use by women who are known to have the following conditions:

- Known or suspected pregnancy
- Known or suspected carcinoma of the breast, or other progestin-sensitive cancer, now or in the past
- Undiagnosed abnormal uterine bleeding
- Hypersensitivity to any component of this product (*see Precautions, FD & C Yellow No. 5*)
- Benign or malignant liver tumors

WARNINGS

1. Ectopic Pregnancy

The incidence of ectopic pregnancies for progestin-only oral contraceptive users is 5 per 1000 woman-years. Up to 10% of pregnancies reported in clinical studies of progestin-only oral contraceptive users are extrauterine. Health-care providers should be alert to the possibility of an ectopic pregnancy in women who become pregnant or complain of lower abdominal pain while on Opill Tablets.

2. Delayed Follicular Atresia/Ovarian Cysts

If follicular development occurs, atresia of the follicle is sometimes delayed, and the follicle may continue to grow beyond the size it would attain in a normal cycle. Generally these enlarged follicles disappear spontaneously. Often they are asymptomatic; in some cases they are associated with mild abdominal pain, and rarely they may twist or rupture, requiring surgical intervention.

3. Bleeding Pattern Alterations

Irregular menstrual patterns are common among women using Opill Tablets. Undiagnosed abnormal uterine bleeding should be evaluated before Opill is prescribed (see Contraindications). In the 8 U.S. clinical trials of Opill Tablets, there were a total of 2,575 enrolled subjects, and approximately half of them experienced some menstrual changes. This was defined in the clinical studies as vaginal bleeding which, in the judgment of the subject, did not have the characteristics of her pre-treatment menstrual periods in duration, amount or appearance. Subjects experienced unscheduled (breakthrough) bleeding (48.6%) and spotting (47.3%) on Opill Tablets. Amenorrhea occurred in 6.1% of subjects in their first cycle and 28.7% of all subjects during the studies. A total of 379 participants (17.4%) discontinued treatment due to side effects; 67.6% of all discontinuations were due to bleeding patterns. Overall, 6.4% of participants discontinued treatment due to breakthrough bleeding and 2.7% due to amenorrhea (n=2,173 subjects who completed at least one cycle).

If uterine bleeding together with the clinical history is suggestive of infection, malignancy, pregnancy, or other conditions, rule out these conditions. If amenorrhea occurs, consider the possibility of pregnancy.

4. Hepatic Neoplasia/Liver Disease

Discontinue Opill Tablet use if jaundice or acute disturbances of liver function develop. Do not resume use until markers of liver function return to normal and Opill Tablet causation has been excluded.

PRECAUTIONS

1. Migraine/Headache

The onset or exacerbation of migraine, or development of headache with a new pattern that is recurrent, persistent, or severe requires evaluation of the cause because women with migraine may be at increased risk of stroke.

2. Drug Interactions

- The effectiveness of progestin-only pills is reduced by hepatic enzyme-inducing drugs such as phenytoin, carbamazepine, barbiturates, rifampin, efavirenz, bosentan and herbal preparations containing St. John's Wort (hypericum perforatum). This could result in unintended pregnancy or breakthrough bleeding.

  During concomitant use of Opill and substances that may affect its efficacy, it is recommended that a nonhormonal back-up method of contraception (such as condom) be used in addition to the regular intake of Opill Tablets. Use of a nonhormonal back-up method is recommended for 28 days after discontinuation of substances that have led to induction of hepatic microsomal enzymes. For women receiving long-term therapy with hepatic enzyme inducers, another method of contraception should be considered.

- Effectiveness of progestin-containing hormonal contraceptives and emergency contraceptive ulipristal acetate may be decreased if progestin-containing hormonal contraceptives are used within five days after ulipristal acetate dosing.

  If a woman wishes to use Opill Tablets after using ulipristal acetate, she should do so no sooner than 5 days after the intake of ulipristal acetate and she should use a reliable barrier method for subsequent acts of intercourse until her next menstrual period.

3. Gastrointestinal

Diarrhea and/or vomiting within 4 hours after taking a pill may reduce hormone absorption. Women should use of a nonhormonal back-up method of birth control (such as a condom or spermicide) during the next 48 hours.

4. Interactions with Laboratory Tests

The following endocrine tests may be affected by Opill Tablets use:

- Sex hormone-binding globulin (SHBG) concentrations may be decreased.
- Total thyroxine concentrations may be decreased, due to a decrease in thyroid binding globulin (TBG). However, free thyroxine level should remain unchanged.

5. FD & C Yellow No. 5

Opill Tablets contains FD&C Yellow No.5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity. (See **CONTRAINDICATIONS**)

6. Carbohydrate and Lipid Effects

Some Opill Tablets users may experience slight changes in glucose tolerance with increases in plasma insulin, but women with diabetes mellitus who use progestin-only oral contraceptives do not generally experience changes in their insulin requirements.

Lipid metabolism is occasionally affected in that HDL1, HDL2, and apolipoprotein A-I and A-II may be decreased; hepatic lipase may be increased. There is usually no effect on total cholesterol, HDL_3, LDL, or VLDL.

The effect of progestin-only oral contraceptives on carbohydrate and lipid metabolism is generally not clinically significant.

7. Pregnancy

Opill Tablets are contraindicated for use in pregnant women because there is no need for pregnancy prevention in a woman who is already pregnant [see Contraindications (4)]. Published studies report no harmful effects on fetal development associated with long-term use of contraceptive doses of oral progestins in pregnant women.

Discontinue Opill Tablets if pregnancy is confirmed.

8. Nursing Mothers

Small amounts of progestin pass into the breast milk, resulting in steroid levels in infant plasma. No adverse effects have been reported on breastfeeding performance or infant health. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Opill Tablets and any potential adverse effects on the breastfed infant from Opill Tablets or from the underlying maternal condition.

9. Fertility Following Discontinuation

The limited available data do not indicate a significant delay in the return of normal ovulation and fertility following discontinuation of progestin-only oral contraceptives.

10. Pediatric Use

Safety and efficacy of Opill Tablets have been established in women of reproductive age, including adolescents as young as 15 years of age, and almost 30% of subjects in the clinical trials who were under 20 years of age. Use of this product before menarche is not indicated.

11. Geriatric Use

Opill Tablets has not been studied in postmenopausal women and is not indicated in this population.

INFORMATION FOR THE PATIENT

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Before prescribing Opill Tablets, advise the patient that:

- Opill Tablets should be taken at the same time every day, including throughout all bleeding episodes.
- She should use a nonhormonal back-up method of contraception (such as condoms or spermicides) for the next 48 hours whenever Opill Tablets are taken 3 or more hours late, or if she has vomiting or diarrhea within 4 hours after taking the pill.
- Use of Opill Tablets may be associated with changes in their normal menstrual bleeding pattern. However, women who miss two periods (or have missed a single period but have missed doses of Opill) or suspect they may be pregnant should take a pregnancy test.

- She should inform her healthcare provider if she develops repeated vaginal postcoital bleeding, prolonged episodes of bleeding, amenorrhea or development of severe abdominal pain.
- Opill Tablets do not protect against HIV infection (AIDS) or other sexually transmitted infections (STIs).

ADVERSE REACTIONS

An increased risk of the following adverse reactions has been reported with the use of progestin-only oral contraceptives (see WARNINGS section for additional information):

- Delayed follicular atresia/ovarian cysts
- Menstrual irregularity, changes in menstrual flow; breakthrough bleeding/spotting; amenorrhea, prolonged bleeding

The following adverse reactions were reported in ≥ 5% of subjects in the Opill Tablet clinical studies:

- Headache
- Dizziness
- Nausea
- Increased appetite
- Abdominal pain, cramps and bloating
- Fatigue
- Vaginal discharge
- Dysmenorrhea
- Nervousness
- Backache
- Breast discomfort
- Acne

OVERDOSAGE

Symptoms of oral contraceptive overdosage may include nausea, vomiting, breast tenderness, dizziness, somnolence (drowsiness/fatigue), and withdrawal bleeding in females. There is no specific antidote and further treatment of overdose, if necessary, is directed to the symptoms.

DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, Opill Tablets must be taken exactly as directed.

The woman should take one tablet every day, at the same time. Administration is continuous, with no interruption between pill packs. See **PATIENT LABELING** for detailed instructions.

HOW SUPPLIED

Opill Tablets (0.075 mg norgestrel) are available in a blister package of 28 tablets as follows: NDC76336-457-28, yellow, round tablet debossed “NG75" on one side.

STORAGE

Store at controlled room temperature between 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Manufactured for:

Laboratoire HRA Pharma

15 rue Béranger – 75003 PARIS France

Patient Information

Opill® *(Oh-Pil)*

(norgestrel tablets), for oral use

Opill does not protect against HIV infection (AIDS) or other sexually transmitted infections (STIs).

What is Opill?

- Opill is a birth control pill for daily use by women to prevent pregnancy.
- Opill tablets are not to be used as emergency contraceptive.
- Opill tablet contain a progestin hormone norgestrel. Progestin-only pills are often called “POPs” or “the minipill.” Opill does not contain estrogen.

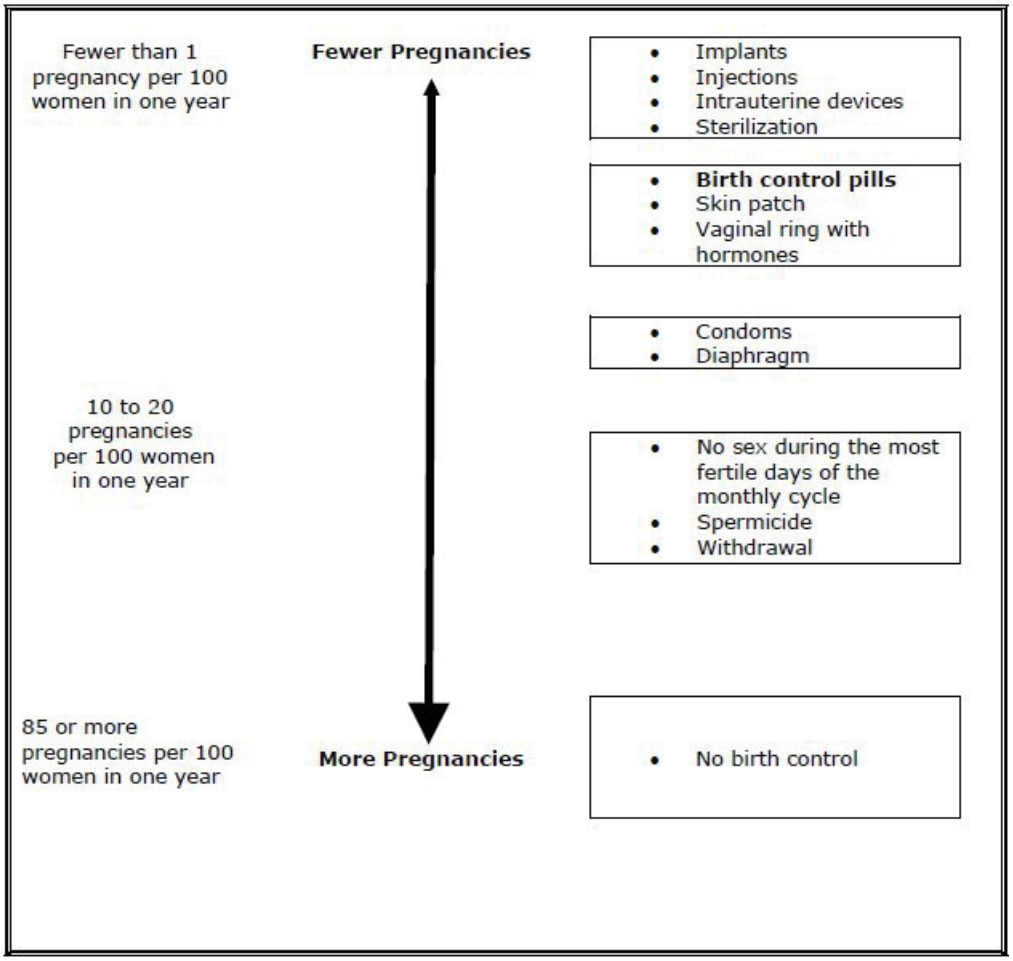
How does Opill work?

- Opill prevents pregnancy in several ways. Opill thickens mucus in your cervix, and this change may keep sperm from reaching the egg. Opill stops the release of an egg from your ovary. Opill also thins the lining of your uterus.

How well does Opill work for contraception?

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.

Opill, a birth control pill, is in the box second to top of the chart.



Do not use Opill if you:

- are or may be pregnant
- have undiagnosed uterine bleeding
- have ever had breast cancer or any other cancer that is sensitive to progestin (a female hormone)
- have liver disease or a liver tumor
- are allergic to norgestrel or any of the ingredients in Opill. See the end of this leaflet for a complete list of ingredients in Opill.

Before taking Opill, tell your healthcare provider if you are taking medicines for:

- seizures (epilepsy), tuberculosis (TB),
- HIV/AIDS
- Pulmonary hypertension
- Emergency contraception (ulipristal acetate 30 mg) in the past 5 days

Consider using another birth control method when you take medicines that may make birth control pills less effective

Tell your healthcare provider about all the medicines you take, including prescription and over-the counter medicines, vitamins, and herbal supplements.

How should I take Opill?

- Opill must be taken **at the same time every day**, so choose a time and then take the pill at that same time every day. If you take a pill late, and especially if you miss a pill, you are more likely to get pregnant (See **What if I am late or miss taking OPILL**.).

What are some important points to remember when taking Opill?

- You may have some bleeding between periods. Do not stop taking your pills if this happens. Bleeding between periods is usually temporary and does not mean there is a problem; however, if you repeatedly have vaginal bleeding that is brought on by sex or bleeding is prolonged (more than 8 days) or unusually heavy, consult your health-care provider.
- If you have not had a menstrual period for 2 months (or you have missed a single period but you have missed doses of Opill) after you have had regular periods or think you may be pregnant, you should have a pregnancy test.
- If you vomit within 4 hours after taking a pill, or have diarrhea, absorption may not be complete; therefore, use a nonhormonal back-up method of birth control (such as a condom or spermicide) every time you have sex during the next 48 hours.

  If you are not sure about how to take Opill, ask your health-care provider.

When can I start Opill?

- You can start taking your first pill on any day, use a non-hormonal back-up method of birth control (such as a condom or spermicide) every time you have sex during the first 48 hours after starting Opill.
- Start the next pack the day after the last pack is finished. There is no break between packs. Always have your next pack of pills ready.
- If you have had a miscarriage or an abortion, you can start Opill the next day. In addition, you should use a non- hormonal back-up method of birth control for the first 48 hours.
- If you gave birth and are NOT breastfeeding, you can start Opill the next day. In addition, you should use a non- hormonal back-up method of birth control for the first 48 hours. If you are breastfeeding see section "**Is it safe to breastfeed while using Opill?**"

What if I want to Switch Pills?

- If you are switching from the combined pills (containing both estrogen and progestogen) to Opill (progestin only), take the first Opill the day after you finish the last active combined pill. Do not take any of the inactive pills from the combined pill pack.
- If you switch to Opill tablets from another brand of POPs, you can start the new pack at any time.

What if I want to change from another type of progestin-only method (IMPLANT, INJECTION) or IUD?

- Start taking Opill on the day of an implant or IUD removal or, if using an injection, the day the next injection would be due. In addition, use a non-hormonal back-up method of birth control for the first 48 hours after starting Opill tablets.

What if I am late or miss taking Opill?

If you are late taking a single pill:

- **If you are less than 3 hours late** from your usual time you take the pill, take 1 pill immediately and go back to taking your pill at your usual time the following day.
- If you are more than 3 hours late:
  - Take 1 pill as soon as you remember and go back to taking your pill at your usual time. This means you may take 2 pills in 1 day.
  - You must use a condom (or another barrier method) every time you have sex during the 2 days (48 hours) after you restart Opill, because it takes 2 days to start working again.

If you miss more than one pill:

- Take the first missed pill as soon as you remember, even if it means you take 2 pills in 1 day. Then continue taking one pill daily at your usual time.
- You must use a condom (or another barrier method) every time you have sex during the 2 days (48 hours) after you restart Opill, because it takes 2 days to start working again.
- If you miss 3 or more pills, consider the possibility that you may be pregnant.
- If you are not sure what to do about the pills you have missed, keep taking Opill and use a condom (or another barrier method) every time you have sex until you can talk to your healthcare provider.

What are the possible side effects of Opill?

- **Changes in menstrual bleeding.** You may have changes in menstrual bleeding, including bleeding and spotting between menstrual periods, or your menstrual periods may stop. Tell your healthcare provider if you have irregular or heavy bleeding, bleeding or spotting that goes on for a long time, spotting in between your periods, or if you have not had a menstrual period for 2 months after having normal periods.
- **Cysts on the ovary.** Some women using OPILL develop a cyst on the ovary. These cysts are small sacs of fluid and usually disappear on their own, but sometimes they can cause pain. Sometimes surgery is needed to remove a cyst on the ovary
- **Allergy. Opill contains FD&C Yellow No. 5 (tartrazine)** which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin sensitivity

The most common side effects of Opill include:

- Headache, Dizziness, Nausea, Increased appetite, Abdominal pain, cramps and bloating, Fatigue, Vaginal discharge, Dysmenorrhea, Nervousness, Backache, Breast discomfort, Acne

These are not all the possible side effects of Opill. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

After I take Opill, when should I call my healthcare provider?

Call your healthcare provider if you have any concerns about Opill.

Call your healthcare provider right away if you:

- think you might be pregnant

- have sudden or severe pain in your belly (you could have an ectopic pregnancy)
- you repeatedly have vaginal bleeding that is brought on by sex
- have heavy vaginal bleeding or bleeding that concerns you
- start having migraines with aura (headaches that start with changes in vision) or your migraines headaches get worse
- have jaundice, yellowing of your skin or whites of your eyes (especially with fever, tiredness, loss of appetite or dark colored urine)

General information about the safe and effective use of Opill

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about Opill that is written for healthcare providers.

What if I want to stop taking Opill?

If you want to stop taking Opill, you can do so at any time, but, if you remain sexually active and don't wish to become pregnant, be certain to use another birth control method.

What are the other ingredients in Opill?

The other ingredients that are present in Opill are cellulose, FD&C Yellow 5, lactose, magnesium stearate, and polacrilin potassium.

Will Opill affect my ability to get pregnant later?

If you want to become pregnant, simply stop taking Opill. Opill will not delay your ability to get pregnant.

What if I become pregnant while using Opill?

Call your healthcare provider right away if you think that you are pregnant. If you get pregnant while using Opill, you may have an ectopic pregnancy. This means that the pregnancy is not in the uterus. Unusual vaginal bleeding or lower stomach area (abdominal) pain may be a sign of ectopic pregnancy.

Ectopic pregnancy is a medical emergency that may require surgery. Ectopic pregnancy can cause internal bleeding, infertility, and even death.

Is it safe to take Opill while Breastfeeding?

The hormone in Opill passes into your breast milk. The health of breastfed children whose mothers used progestin only pills has been studied. No effects on the growth and development of the children or on breast milk were seen. Discuss with your healthcare provider when to start birth control after having your baby.

How should I Store Opill?

Store Opill at room temperature between 20° to 25°C (68° to 77°F).

This Patient Information has been approved by the US Food and Drug Administration.

Revised: August 2017

Manufactured for:
Laboratoire HRA Pharma
15 rue Béranger – 75003 PARIS France

5.2 Proposed Carton Labeling Submitted in sNDA (PDP and DFL Version H per Applicant)

Figure 1. Proposed Carton Labeling Submitted in sNDA (PDP and DFL Version H per Applicant)

Source: norgestrel-0-075-mg-1-28-tablets-carton-label, Module 1.14.1.1.1.1, NDA 017031 S-041 stamp date June 14, 2022

5.3 Proposed Drug Facts Label Submitted in sNDA (DFL Version H per Applicant)

Figure 2. Proposed Drug Facts Label Submitted in sNDA (DFL Version H per Applicant)

Drug Facts

Active Ingredient (in each tablet)	***Purpose***
Norgestrel 0.075 mg	Daily Oral Contraceptive

Use

To prevent pregnancy

Warnings

Allergy alert: Do not use if you are allergic to this product or any of its ingredients, such as FD&C yellow No.5 (tartrazine). People allergic to aspirin often have a tartrazine allergy too. Symptoms may include hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.

Sexually Transmitted diseases (STDs) alert: This product does **not** protect against HIV/AIDS or other STDs.

Do not use

- if you **have or ever had** breast cancer
- if you are already pregnant or think you may be pregnant
- together with another birth control pill, vaginal ring, patch, implant, injection or an IUD (intra-uterine device)
- as an emergency contraceptive (morning after pill). This product does not prevent pregnancy when used after unprotected sex
- if you are male

Ask a doctor before use if

- you currently have unexplained vaginal bleeding between your periods and you have not already talked to a doctor
- you have liver problems
- you **have or ever had** any cancer

Ask a doctor or pharmacist before use if

- you are taking a prescription drug for seizures, tuberculosis, HIV/AIDS, pulmonary hypertension
- you are taking a supplement containing St John's Wort (an herbal ingredient)
- you have taken ulipristal acetate (an emergency contraceptive, or morning after pill) in the past 5 days

See the enclosed leaflet for a detailed list of medicines that may interact with this product.

Drug Facts (continued)

When using this product

- **you are likely to experience changes in your menstrual periods**, such as irregular periods, spotting or bleeding between your periods, or you may stop having periods. To prevent pregnancy, keep taking the product.
- you may experience headaches, dizziness, nausea, increased appetite, abdominal pain, cramps or bloating
- **talk to a doctor (but continue taking every day) if**
  - you have repeated vaginal bleeding brought on by sex
  - you start having periods that last more than 8 days or are unusually heavy
  - you start having migraines with aura (headaches that start with changes in vision) or your migraine headaches get worse
- **take a pregnancy test or talk to a doctor if**
  - your period is late after missing any tablets in the last month
  - you have not had a period for 2 months or think you may be pregnant

Seek medical help right away if

- you have sudden or severe persistent pain in your lower belly mostly on one side (you could have an ectopic pregnancy)
- you develop yellowing of your skin or whites of your eyes especially with fever, tiredness, loss of appetite or dark colored urine

Stop use and ask a doctor if

- you become pregnant

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **take 1 tablet** ***at the same time every day***
  - this product will work best to prevent pregnancy when taken exactly as directed
  - you can start on any day of the month
  - use a condom (or another barrier method) every time you have sex during the first 2 days of use (48 hours) after you start your first pack of this product, because it takes 2 days for this product to start working

  See the enclosed leaflet for more information on how to switch from another contraceptive method

Drug Facts (continued)

Directions *(continued)*

- **never skip your daily tablet**
  - to prevent pregnancy, take this product every day, even when you bleed or have spotting
  - when you finish this pack, start the next one the following day without a break
- **if you are more than 3 hours late taking your tablet or miss taking your tablet** on 1 or more days:
  - take 1 tablet immediately, as soon as you remember that you missed it
  - then go back to taking your daily tablet at your usual time
  - use a condom (or another barrier method) every time you have sex during the next 2 days (48 hours), because it takes 2 days for this product to start working again
- **if you vomit** for any reason **or have severe diarrhea within 4 hours** of taking your daily tablet, use a condom (or another barrier method) every time you have sex for the next 2 days (48 hours), because the medicine may not have been fully absorbed
- you should continue to see your healthcare provider(s) for routine healthcare visits

When to use a condom (or another barrier method)

- every time you have sex for the next 2 days (48 hours):
  - after you start your first pack of this product
  - if you take a tablet more than 3 hours late or miss a tablet on 1 or more days
  - if you vomit or have severe diarrhea within 4 hours of taking a tablet

Other information

- contains FD&C yellow No.5 (tartrazine) as a color additive
- **read the instructions, warnings and enclosed product leaflet before use**
- as with any birth control method, this product does not prevent pregnancy all the time
- this product will work best if you take it exactly as directed
- store between 20°-25°C (68°-77°F)

Inactive Ingredients

cellulose, FD&C Yellow No.5, lactose, magnesium stearate, polacrilin potassium

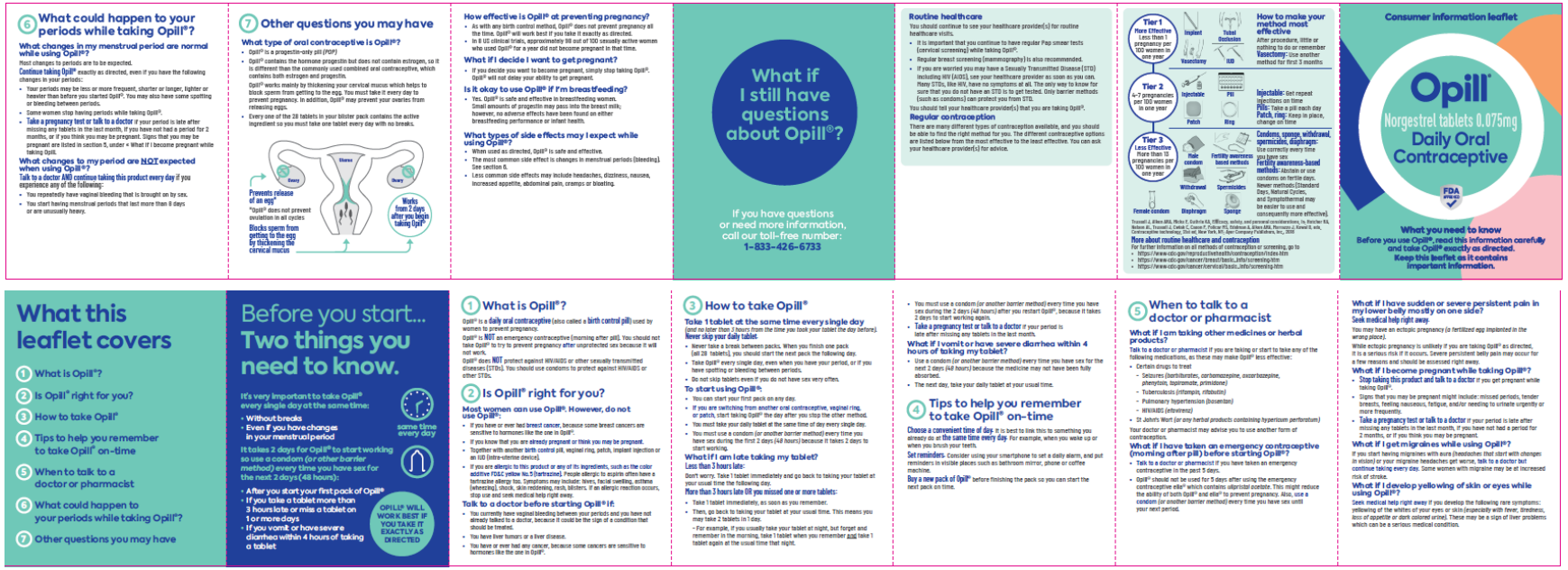
☎ ***Questions or comments?***

Call 1-833-426-6733

Source: draft-labeling-test-dfl, Module 1.14.1.3.1, NDA 017031 S-041 stamp date June 14, 2022

5.4 Proposed Consumer Information Leaflet Submitted in sNDA

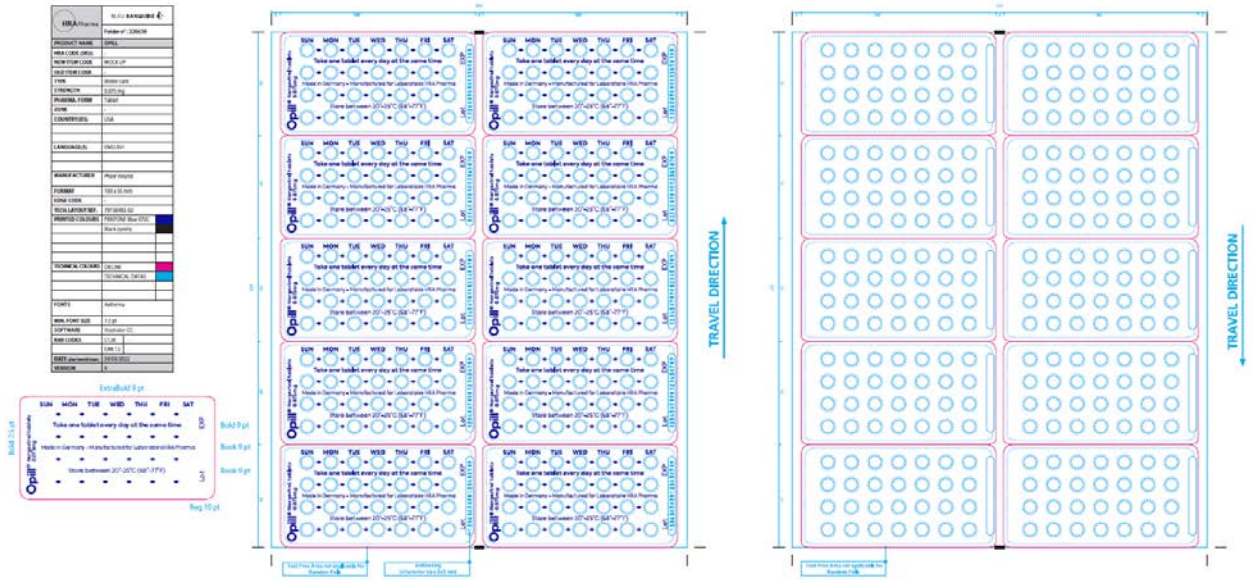
Figure 3. Proposed Consumer Information Leaflet Submitted in sNDA



Source: norgestrel-0-075-mg-1-28-tablets-carton-label, Module 1.14.1.1.3, NDA 017031 S-041 stamp date June 14, 2022

5.5 Proposed Labeling for Blister Package Submitted in sNDA

Figure 4. Proposed Labeling for Blister Package Submitted in sNDA



Source: norgestrel-0-075-mg-blister-label, Module 1.14.1.1.2.1, NDA 017031 S-041 stamp date June 14, 2022

5.6 Carton Labeling Used in ACCESS (PDP and DFL Version F per Applicant)

Figure 5. Opill Carton Labeling Used in ACCESS (PDP and DFL Version F per Applicant)

Source: Section 16.1.1 ACCESS Clinical Study Report, Adherence with Continuous-dose Oral Contraceptive: Evaluation of Self-Selection and Use (ACCESS) Protocol, Module 5.3.5.2, NDA 017031 S-041 stamp date June 14, 2022

5.7 Consumer Information Leaflet Used in ACCESS

Figure 6. Opill Consumer Information Leaflet Used in ACCESS

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5 When to Talk to a Doctor or Pharmacist p. 6
6 What Could Happen to Your Periods While Taking Opill®? p. 8
7 Other Questions You May Have p. 9

It's Very Important

It's very important to take Opill® every single day at the same time:
- without breaks
- even if you have changes in your menstrual period

It takes 2 days for Opill® to start working so:
use a condom *(or other barrier method)* every time you have sex for the next 2 days:
- after starting Opill®
- if you are more than 3 hours late taking your daily pill or miss one or more pills
- if you vomit or have diarrhea within 4 hours of taking your daily pill

OPILL® WILL WORK BEST IF YOU TAKE IT EXACTLY AS DIRECTED

1

1 What is Opill®?

- Opill® is a **daily birth control** pill used by women to prevent pregnancy.
- Opill® is **NOT** an emergency contraceptive. You should not take Opill® to try to prevent pregnancy **after** unprotected sex because it will not work.

2 Is Opill® Right for You?

Most women can use Opill®. However, do not use:
- If you have or ever had **breast cancer**, because some breast cancers are sensitive to hormones like those in Opill®.
- If you know that you are **already pregnant or think you may be pregnant.**
- Together with **another birth control** pill, vaginal ring, patch, implant, injection or an IUD (intra-uterine device).

Talk to a doctor before starting Opill® if:
- You have liver tumors or a liver disease.
- You have unexplained vaginal bleeding between your periods.

2

3 How to Take Opill®

Take 1 tablet at the same time every single day (and no later than 3 hours from the time you took your pill the day before).

Never skip your daily pill.
- Never take a break between packs. When you finish one pack *(all 28 pills)*, you should start the next pack the following day.
- Take Opill® every single day, even when you have your period, or if you have spotting or bleeding between periods.
- Do not skip pills even if you do not have sex very often.

To start using Opill®:
- You can start your first pack on any day.
- If you are switching from another birth control pill, vaginal ring, or patch, start taking Opill® the day after you stop the other method.
- You must take your daily pill at the same time of day every single day.
- You must use a condom *(or another barrier method)* every time you have sex during the first 2 days *(48 hours)*.

3

What if I am late taking my pill?

Less than 3 hours late:
- Don't worry. Take 1 pill immediately and go back to taking your pill at your usual time the following day.

More than 3 hours late OR you missed one or more pills:
- Take 1 pill immediately, as soon as you remember
- Then, go back to taking your pill at your usual time. This means you may take 2 pills in 1 day.
  - For example, if you usually take your pill at night, but forget and remember in the morning, take 1 pill when you remember and take 1 pill again at the usual time that night.
- You must use a condom *(or another barrier method)* every time you have sex during the 2 days *(48 hours)* after you restart Opill®, because it takes 2 days to start working again.

What if I vomit or have severe diarrhea within 4 hours of taking my pill?
- Use a condom *(or another barrier method)* every time you have sex for the next 2 days *(48 hours)* because the medicine may not have been fully absorbed.
- The next day, take your daily pill at your usual time.

4

4 Tips to Help You Remember to Take Opill® On Time

- **Choose a convenient time of day.** It is best to link this to something you already do at **the same time every day**. For example, when you wake up or when you brush your teeth.
- **Set an alarm.** Consider using your smartphone to set an alarm and the reminder stickers included in your pack.
- **Buy a new pack of Opill®** a few days before finishing the pack, so you can start the next pack on time.

5

5 When to Talk to a Doctor or Pharmacist

What if I am taking other medicines or herbal products?

Talk to a doctor or pharmacist if you are taking or start to take any of the following, as these may make Opill® less effective:

- Certain drugs to treat:
  - Seizures *(barbiturates, carbamazepine, oxcarbazepine, phenyton, topiramate, primidone)*
  - Tuberculosis *(rifampicin, rifabutin)*
  - Pulmonary hypertension *(bosentan)*
  - HIV / AIDS
- St. John's Wort *(or any herbal products containing hypericum perforatum)*

What if I have taken an emergency contraceptive before starting Opill®?

- **Talk to a doctor or pharmacist** if you have taken an emergency contraceptive in the past 5 days.
- Opill® should not be used for 5 days after using the emergency contraceptive ella® *(which contains ulipristal acetate)*. This might reduce the ability of both Opill® and ella® to prevent pregnancy. Also, **use a condom** *(or another barrier method)* every time you have sex until your next period.

6

What if I have sudden or severe abdominal pain in my lower belly?

Contact a doctor immediately.

You may have an ectopic pregnancy *(a fertilized egg implanted in the wrong place)*.

What if I become pregnant while taking Opill®?

- **Stop taking this product and talk to a doctor** if you get pregnant while taking Opill®.
- Signs that you may be pregnant might include: missed periods, tender breasts, feeling nauseous, fatigue, and/or needing to urinate urgently or more frequently.
- If you have not had a menstrual period for two months, you may be pregnant. **Do a pregnancy test or talk to a doctor.**

What if I get migraines while using Opill®?

- If you start having migraines with aura *(headaches that start with changes in vision)* or your migraine headaches get worse, **talk to a doctor**, as some women with migraine may be at increased risk of stroke.

What if I develop yellowing of skin or eyes while using Opill®?

- **Stop use and ask a doctor** if you develop the following rare symptoms – yellowing of the whites of your eyes or skin *(especially with fever, tiredness, loss of appetite or dark colored urine)*.

7

6 What Could Happen to Your Periods While Taking Opill®?

What changes in my menstrual period are normal while using Opill®?

Most changes to periods are to be expected.

Continue taking Opill® exactly as directed, even if you have the following changes in your periods:

- Your periods may be less or more frequent, shorter or longer, lighter or heavier than before you started Opill®. You may also have some spotting or bleeding between periods.
- Some women stop having periods while taking Opill®. If you haven't had a period in 2 months, **take a pregnancy test or talk to a doctor.**

What changes to my period are NOT expected when using Opill®?

Talk to a doctor while continuing to take this product every day even if you experience any of the following:

- You had unexplained vaginal bleeding between your periods before you started this product.
- You repeatedly have bleeding that is brought on by sex.
- Your menstrual period lasts more than 8 days or is unusually heavy.

8

7 Other Questions You May Have

What type of birth control is Opill®?

- Opill® is a progestin-only pill *(POP)*.
- Opill® contains the hormone progestin but does not contain estrogen, so it is different than the commonly used combined birth control pill, which contains both estrogen and progestin.
- Every one of the 28 pills in your blister pack contains the active ingredient, so you must take one pill every day with no breaks.

How effective is Opill®?

- As with any birth control method, Opill® does not prevent pregnancy all the time. Opill® will work best if you take it exactly as directed.
- In 8 US clinical trials, approximately 98 out of 100 sexually active women who used Opill® for a year did not become pregnant in that time.

9

What if I decide I want to get pregnant?

- If you decide you want to become pregnant, simply stop taking Opill®. Opill® will not delay your ability to get pregnant.

Is it okay to use Opill® if I'm breastfeeding?

- Yes. Opill® is safe and effective in breastfeeding women. Small amounts of progestin may pass into the breast milk; however, no adverse effects have been found on either breastfeeding performance or infant health.

What types of side effects may I expect while using Opill®?

- When used as directed, Opill® is safe and effective.
- The most common side effect is changes in menstrual period (bleeding). See previous section 6.
- Less common side effects may include headaches, dizziness, nausea, increased appetite, abdominal pain, cramps or bloating.

What if I still have questions about Opill®?

If you have questions or need more information, call our toll-free number, 1-800-XXX-XXX, or visit our website at www.XXXX.com.

46402

10

consumer information leaflet

Opill®

daily birth control

(norgestrel) tablets 0.075mg

What You Need to Know

Before you use Opill®, read this information carefully and take Opill® exactly as directed.

Keep this leaflet as it contains important information.

Source: Section 16.1.1 ACCESS Clinical Study Report, Adherence with Continuous-dose Oral Contraceptive: Evaluation of Self-Selection and Use (ACCESS) Protocol, Module 5.3.5.2, NDA 017031 S-041 stamp date June 14, 2022

5.8 Carton Labeling Used in Combined Label Comprehension Study/Targeted Breast Cancer Self-Selection Study (PDP and DFL Version G per Applicant)

Figure 7. Opill Carton Labeling Used in Combined Label Comprehension Study/Targeted Breast Cancer Self-Selection Study (PDP and DFL Version G per Applicant)

Drug Facts

Active ingredient (in each tablet)	*Purpose*
Norgestrel 0.075 mg	Daily Oral Contraceptive

USE

To prevent pregnancy

Warnings

Allergy alert: Do not use if you are allergic to this product or any of its ingredients, such as FD&C yellow No.5 (tartrazine). People allergic to aspirin often have a tartrazine allergy too. Symptoms may include hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.

Sexually transmitted diseases (STDs) alert: This product does **not** protect against HIV/AIDS or other STDs.

Do not use

- if you **have or ever had** breast cancer
- if you are already pregnant or think you may be pregnant
- together with another birth control pill, vaginal ring, patch, implant, injection or an IUD (intra-uterine device)
- as an emergency contraceptive (morning after pill). This product does not prevent pregnancy when used after unprotected sex
- if you are male

Ask a doctor before use if

- you currently have vaginal bleeding between your periods and you have not already talked to a doctor
- you have liver problems
- you **have or ever had** any cancer

Ask a doctor or pharmacist before use if

- you are taking a prescription drug for seizures, tuberculosis, HIV/AIDS, pulmonary hypertension
- you are taking a supplement containing St John's Wort (an herbal ingredient)
- you have taken ulipristal acetate (an emergency contraceptive, or morning after pill) in the past 5 days.

See the enclosed leaflet for a complete list of medicines that may interact with this product. ▶

LIFT FLAP

Drug Facts (continued)

When using this product

- **you are likely to experience changes in your menstrual periods**, such as irregular periods, spotting or bleeding between your periods, or you may stop having periods. To prevent pregnancy, keep taking the product.
- you may experience headaches, dizziness, nausea, increased appetite, abdominal pain, cramps or bloating
- **talk to a doctor (but continue taking every day) if**
  - you have repeated vaginal bleeding brought on by sex
  - you start having periods that last more than 8 days or are unusually heavy
  - you start having migraines with aura (headaches that start with changes in vision) or your migraine headaches get worse
- **take a pregnancy test or talk to a doctor if**
  - your period is late after missing any tablets in the last month
  - you have not had a period for 2 months or think you may be pregnant

Seek medical help right away if

- you have sudden or severe persistent pain in your lower belly mostly on one side (you could have an ectopic pregnancy)
- you develop yellowing of your skin or whites of your eyes especially with fever, tiredness, loss of appetite or dark colored urine

Stop use and ask a doctor if

- you become pregnant

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **take 1 tablet *at the same time every day***
  - this product will work best to prevent pregnancy when taken exactly as directed
  - you can start on any day of the month
  - use a condom (or another barrier method) every time you have sex during the first 2 days of use (48 hours) after you start your first pack of this product, because it takes 2 days for this product to start working

See the enclosed leaflet for more information on how to switch from another contraceptive method. ▶

Drug Facts (continued)

***Directions** (continued)*

- never skip your daily tablet
  - to prevent pregnancy, take this product every day, even when you bleed or have spotting
  - when you finish this pack, start the next one the following day without a break
- if you are more than 3 hours late taking your tablet or miss taking your tablet on 1 or more days:
  - take 1 tablet immediately, as soon as you remember that you missed it
  - then go back to taking your daily tablet at your usual time
  - use a condom (or another barrier method) every time you have sex during the next 2 days (48 hours), because it takes 2 days for this product to start working again
- **if you vomit** for any reason or **have severe diarrhea within 4 hours** of taking your daily tablet, use a condom (or another barrier method) every time you have sex for the next 2 days (48 hours), because the medicine may not have been fully absorbed

When to use a condom (or another barrier method)

- every time you have sex for the next 2 days (48 hours):
  - after you start your first pack of this product
  - if you take a tablet more than 3 hours late or miss a tablet on 1 or more days
  - if you vomit or have a severe diarrhea within 4 hours of taking a tablet

Other information

- as with any birth control method, this product does not prevent pregnancy all the time
- this product will work best if you take it exactly as directed
- you should continue to see your healthcare provider(s) for routine healthcare visits
- **read the instructions, warnings and enclosed product leaflet before use**
- contains FD&C yellow No.5 (tartrazine) as a color additive
- store between 20°-25°C (68°-77°F)

Inactive ingredients

cellulose, FD&C Yellow No. 5, lactose, magnesium stearate, and polacrilin potassium

☎ ***Questions or Comments?***

Call 1-800-XXX-XXXX or visit www.xxx.com

Source: Study to Test the Self-Selection and Comprehension of the Opill OTC Drug Facts Label, Protocol, Module 1.14.1.4, NDA 017031 S-041 stamp date June 14, 2022

5.9 Delayed Pill Intake Study Supplemental Information (151042-002)

The study enrolled healthy premenopausal females between the ages of 18 and 35 years inclusive with baseline BMI <32 kg/m^2, regular menses, and at least one progesterone concentration >3 ng/mL during the luteal phase of the screening period. Efficacy evaluations included cervical mucus scores (primary), "ovarian activity scores" (secondary), and LNG concentrations (secondary). Safety evaluations included documentation and follow-up of adverse events, bleeding patterns, and laboratory parameters.

A total of 50 females completed all visits in period 1 (where study participants were instructed to take the product at exactly the same time every day), 47 females completed all visits in the delayed tablet period, and 46 females completed all visits in the missed tablet period (8 visits per period). The majority of study participants had a baseline BMI <25 kg/m^2. Eighteen study participants had a BMI above

25 kg/m^2 (34.6%), including 4 study participants with a BMI above 30 kg/m^2 (7.7%). The majority of females identified as white (38/52, 73.1%) whereas the remaining identified as Asian (5/52, 9.6%), Black or African American (2/52, 3.8%), or Other (7/52, 13.5%).

No significant changes in cervical mucus scores or "ovarian activity" score occurred between the perfect use, 6-hour delayed, or missed tablet periods. LNG trough concentrations decreased when administration of the proposed norgestrel product was delayed by 6 or 24 hours (see Clinical Pharmacology review for details). No serious adverse events occurred. Study participants most frequently reported bleeding irregularities (44/52, 84.6%) during the study.

Overall, the findings of this Phase 2 PD study are consistent with the known PK profile and PD effects of norgestrel 0.075 mg.

To establish PK/PD correlation, extensive PK sampling and correlation of PD effects with PK measurements would be necessary. Absence of this data, as well as wide variability in LNG PK measurements and homogeneity of the study population, preclude meaningful conclusions regarding the impact of a delayed or missed tablet on PD parameters.

5.10 Label Comprehension Study of Drug Facts Label Tables

Table 10. Label Comprehension Study of Drug Facts Label (DFL): Demographics

Demographic Characteristic	Label Comprehension Population (N=477)
Age distribution	
Mean (SD)	27.0 (11.0)
Median	26
Range (min, max)	(11, 50)
Age group (years)	
11-14	74 (15.5%)
15-17	78 (16.4%)
18-24	66 (13.8%)
25-45	241 (50.5%)
46+	18 (3.8%)
Adult education level	
Eighth grade or less	0 (0.0%)
Some high school	2 (0.4%)
High school graduate or GED	25 (5.2%)
Some college or technical school	88 (18.4%)
College graduate	146 (30.6%)
Post-graduate college degree	64 (13.4%)
Refused	0 (0.0%)
Adolescent education level	
Seventh grade or less	48 (10.1%)
Eighth grade	26 (5.5%)
Ninth grade (freshman in high school)	19 (4.0%)
Tenth grade (sophomore in high school)	16 (3.4%)
Eleventh grade (junior in high school)	30 (6.3%)
Twelfth grade (senior in high school)	2 (0.4%)
High school graduate, GED, or certificate	5 (1.0%)
Some college or technical school	6 (1.3%)
College graduate	0 (0.0%)
Refused	0 (0.0%)
Ethnicity	

Demographic Characteristic	Label Comprehension Population (N=477)
Hispanic or Latinx	55 (11.5%)
Not Hispanic or Latinx	422 (88.5%)
Refused	0 (0.0%)
Race[1]	
White	276 (57.9%)
Black or African American	140 (29.4%)
Asian	70 (14.7%)
Native Hawaiian or Other Pacific Islander	2 (0.4%)
American Indian or Alaska Native	11 (2.3%)
Other	12 (2.5%)
Refused	0 (0.0%)
Household income	
Less than $25,000	43 (9.0%)
$25,001-$50,000	76 (15.9%)
$50,001-$75,000	118 (24.7%)
$75,001-$100,000	100 (21.0%)
$100,001-$150,000	67 (14.0%)
More than $150,000	37 (7.8%)
Refused	36 (7.5%)
Health literacy[2]	
Normal	351 (73.6%)
Low	126 (26.4%)
Refused REALM/unknown health literacy	0 (0.0%)
History of HBC use	
History of HBC use and OC use	227 (47.6%)
History of HBC use but no OC use	45 (9.4%)
No history of HBC use	205 (43.0%)

Source: Applicant's Study Report.

[1] Answers are not mutually exclusive.

[2] Normal: Participants scoring ≥61 on the REALM or REALM Teen test. Low: Participants scoring ≤60 on the REALM or REALM-Teen test.

Abbreviations: GED, general educational development; HBC, hormonal birth control; OC, oral contraceptive; REALM, Rapid Estimate of Adult Literacy in Medicine

Table 11. Label DFL Comprehension Study of DFL: Analysis of Primary and Secondary Endpoints

Endpoint Type	Endpoint Name	Reviewer or Applicant Reported	Total N=477	NL N=351	LL N=126	Age 11-14 N=74	Age 15-17 N=78	Age 18-50 N=325	History of HBC/OC N=227	History of HBC/No OC N=45	No History of HBC N=205
Primary	A. Q5 and Q5a (b) (6) Do not use if you have or ever had breast cancer	Reviewers	83.7 (80.0, 86.9)	84.1 (79.8, 87.7)	82.5 (74.8, 88.7)	96.0 (88.6, 99.2)	89.7 (80.8, 95.5)	79.4 (74.5, 83.7)	83.7 (78.2, 88.3)	77.8 (62.9, 88.8)	84.9 (79.2, 89.5)
Primary	B. Q6 and Q6a (b) (6) Do not use together with another birth control pill, vaginal ring, patch, implant, injection or IUD	Applicant & reviewers	93.5 (90.9, 95.5)	96.3 (93.7, 98.0)	85.7 (78.4, 91.3)	87.8 (78.2, 94.3)	92.3 (84.0, 97.1)	95.1 (92.1, 97.2)	96.0 (92.6, 98.2)	88.9 (75.9, 96.3)	91.7 (87.1, 95.1)
Primary	C. Q3 ((b) (6) Ask a doctor before use if you currently have vaginal bleeding between your periods and you have not already talked to a doctor	Reviewers	86.0 (82.5, 89.0)	87.2 (83.2, 90.5)	82.5 (74.8, 88.7)	82.4 (71.8, 90.3)	80.8 (70.3, 88.8)	88.0 (84.0, 91.3)	86.3 (81.2, 90.5)	86.7 (73.2, 95.0)	85.4 (79.8, 89.9)
Primary	D. Q16 and 16a (b) (6) Seek medical help right away if: you have sudden or severe persistent pain in your lower belly mostly on one side (you could have an ectopic pregnancy)	Reviewers	93.9 (91.4, 95.9)	96.6 (94.1, 98.2)	86.5 (79.3, 91.9)	91.9 (83.2, 97.0)	94.9 (87.4, 98.6)	94.2 (91.0, 96.4)	94.7 (91.0, 97.2)	88.9 (76.0, 96.3)	94.2 (90.0, 96.9)
Primary	E. Q13 and Q13a (b) (6) Seek medical help right away if: you develop yellowing of your skin or whites of your eyes especially with fever, tiredness, loss of appetite or dark colored urine	Applicant & reviewers	97.5 (95.6, 98.7)	99.1 (97.5, 99.8)	92.9 (86.9, 96.7)	93.2 (84.9, 97.8)	98.7 (93.1, 100.0)	98.2 (96.0, 99.3)	98.7 (96.2, 99.7)	93.3 (81.7, 98.6)	97.1 (93.7, 98.9)

Endpoint Type	Endpoint Name	Reviewer or Applicant Reported	Total N=477	NL N=351	LL N=126	Age 11-14 N=74	Age 15-17 N=78	Age 18-50 N=325	History of HBC/OC N=227	History of HBC/No OC N=45	No History of HBC N=205
Primary	F.Q17 and Q17a and Q17b ((b) (6)) Directions: take 1 tablet…every day	Applicant & reviewers	99.2 (97.9, 99.8)	99.4 (98.0, 99.9)	98.4 (94.4, 99.8)	97.3 (90.6, 99.7)	100 (95.4, 100.0)	99.4 (97.8, 99.9)	99.1 (96.9, 99.9)	97.8 (88.2, 99.9)	99.5 (97.3, 100.0)
Primary	G. Q17 and Q17a and Q17b (b) (6) Directions: take…at the same time every day	Applicant & reviewers	97.5 (95.6, 98.7)	98.9 (97.1, 99.7)	93.7 (87.9, 97.2)	93.2 (84.9, 97.8)	100 (95.4, 100.0)	97.8 (95.6, 99.1)	98.7 (96.2, 99.7)	93.3 (81.7, 98.6)	97.1 (93.7, 98.9)
Primary	H. Q23 and Q23a and Q23b Directions / When to use a condom (or another barrier method): use a condom (or another barrier method) every time you have sex during the first 2 days of use (48 hours) after you start your first pack of this product, because it takes 2 days for this product to start working	Applicant & reviewers	87.2 (83.9, 90.1)	89.5 (85.8, 92.5)	81.0 (73.0, 87.4)	79.7 (68.8, 88.2)	93.6 (85.7, 97.9)	87.4 (83.3, 90.8)	90.7 (86.2, 94.2)	75.6 (60.5, 87.1)	85.9 (80.3, 90.3)
Primary	I. Q29 (b) (6) Directions: to prevent pregnancy, take this product every day, even when you bleed or have spotting	Reviewers	96.4 (94.4, 97.9)	98.0 (95.9, 99.2)	92.1 (85.9, 96.1)	89.2 (79.8, 95.2)	98.7 (93.1, 100.0)	97.5 (95.2, 98.9)	98.2 (95.6, 99.5)	93.3 (81.7, 98.6)	95.1 (91.2, 97.6)
Primary	J. Q22 (b) (6) Directions: when you finish this pack, start the next one the following day without a break	Applicant & reviewers	91.6 (88.8, 93.9)	94.9 (92.0, 96.9)	82.5 (74.8, 88.7)	78.4 (67.3, 87.1)	96.2 (89.2, 99.2)	93.5 (90.3, 96.0)	96.9 (93.7, 98.8)	86.7 (73.2, 94.9)	86.8 (81.4, 91.1)

Endpoint Type	Endpoint Name	Reviewer or Applicant Reported	Total N=477	NL N=351	LL N=126	Age 11-14 N=74	Age 15-17 N=78	Age 18-50 N=325	History of HBC/OC N=227	History of HBC/No OC N=45	No History of HBC N=205
Primary	K. Q27 and Q27a and Q27b (b) (6) Directions: if you are more than 3 hours late taking your tablet or miss taking your tablet on 1 or more days: take 1 tablet immediately, as soon as you remember that you missed it	Applicant & reviewers	97.1 (95.1, 98.4)	98.6 (96.7, 99.5)	92.9 (86.9, 96.7)	94.6 (86.7, 98.5)	98.7 (93.1, 100.0)	97.2 (94.8, 98.7)	98.2 (95.5, 99.5)	91.1 (78.8, 97.5)	97.1 (93.7, 98.9)

Endpoint Type	Endpoint Name	Reviewer or Applicant Reported	Total N=477	NL N=351	LL N=126	Age 11-14 N=74	Age 15-17 N=78	Age 18-50 N=325	History of HBC/OC N=227	History of HBC/No OC N=45	No History of HBC N=205
Primary	L. Q27 and Q27a and Q27b (b) (6) Directions: if you are more than 3 hours late taking your tablet or miss taking your tablet on 1 or more days: then go back to taking your daily tablet at your usual time	Applicant & Reviewers	83.2 (79.6, 86.5)	86.6 (82.6, 90.0)	73.8 (65.2, 81.2)	68.9 (57.1, 79.2)	82.1 (71.7, 89.8)	86.8 (82.6, 90.3)	86.3 (81.2, 90.5)	84.4 (70.5, 93.5)	79.5 (73.3, 84.8)
Primary	M. Q23 and Q23a and Q23b Directions / When to use a condom (or another barrier method): if you are more than 3 hours late taking your tablet or miss taking your tablet on 1 or more days: use a condom (or another barrier method) every time you have sex during the next 2 days (48 hours), because it takes 2 days for this product to start working again	Applicant & reviewers	83.2 (79.6, 86.5)	87.7 (83.9, 91.0)	70.6 (61.9, 78.4)	66.2 (54.3, 76.8)	88.5 (79.2, 94.6)	85.8 (81.6, 89.4)	91.2 (86.7, 94.5)	73.3 (58.1, 85.4)	76.6 (70.2, 82.2)
Primary	N. Q23 and Q23a and Q23b Directions / When to use a condom (or another barrier method): if you vomit for any reason or have severe diarrhea within 4 hours of taking your daily tablet, use a condom (or another barrier method) every time you have sex for the next 2 days (48 h), because the medicine may not have been fully absorbed	Applicant & reviewers	85.1 (81.6, 88.2)	90.3 (86.7, 93.2)	70.6 (61.9, 78.4)	74.3 (62.8, 83.8)	92.3 (84.0, 97.1)	85.8 (81.6, 89.4)	89.9 (85.2, 93.5)	77.8 (62.9, 88.8)	81.5 (75.5, 86.5)

Endpoint Type	Endpoint Name	Reviewer or Applicant Reported	Total N=477	NL N=351	LL N=126	Age 11-14 N=74	Age 15-17 N=78	Age 18-50 N=325	History of HBC/OC N=227	History of HBC/No OC N=45	No History of HBC N=205
Secondary	A. Q1 Purpose and use: Daily oral contraceptive to prevent pregnancy	Applicant & reviewers	98.7 (97.3, 99.5)	99.7 (98.4, 100.0)	96.0 (91.0, 98.7)	93.2 (84.9, 97.8)	98.7 (93.1, 100.0)	100 (98.9, 100.0)	99.1 (96.9, 99.9)	100 (92.1, 100.0)	98.0 (95.1, 99.5)

Endpoint Type	Endpoint Name	Reviewer or Applicant Reported	Total N=477	NL N=351	LL N=126	Age 11-14 N=74	Age 15-17 N=78	Age 18-50 N=325	History of HBC/OC N=227	History of HBC/No OC N=45	No History of HBC N=205
Secondary	B. Q4 and Q4a (b) (6) Do not use if you are allergic to FD&C yellow No.5 (tartrazine)	Applicant & reviewers	93.9 (91.4, 95.9)	95.2 (92.4, 97.2)	90.5 (84.0, 95.0)	89.2 (79.8, 95.2)	96.2 (89.2, 99.2)	94.5 (91.4, 96.7)	95.2 (91.5, 97.6)	91.1 (78.8, 97.5)	93.2 (88.8, 96.2)
Secondary	C. Q2 and Q2a (b) (6) Do not use: if you are already pregnant or think you may be pregnant	Applicant & reviewers	92.0 (89.2, 94.3)	93.2 (90.0, 95.6)	88.9 (82.1, 93.8)	89.2 (79.8, 95.2)	92.3 (84.0, 97.1)	92.6 (89.2, 95.2)	94.3 (90.4, 96.9)	86.7 (73.2, 94.9)	90.7 (85.9, 94.3)
Secondary	D. Q26 and Q26a (b) (6) Do not use: as an emergency contraceptive (morning after pill). This product does not prevent pregnancy when used after unprotected sex	Reviewers	75.5 (71.4, 79.3)	82.1 (77.6, 85.9)	57.1 (48.0, 65.9)	56.8 (44.7, 68.2)	73.1 (61.8, 82.5)	80.3 (75.6, 84.5)	86.3 (81.2, 90.5)	68.9 (53.4, 81.8)	64.9 (57.9, 71.4)
Secondary	E. Q9 and Q9a (b) (6) Do not use: if you are male	Applicant & reviewers	97.3 (95.4, 98.5)	98.0 (95.9, 99.2)	95.2 (89.9, 98.2)	97.3 (90.6, 99.7)	97.4 (91.0, 99.7)	97.2 (94.8, 98.7)	97.8 (94.9, 99.3)	93.3 (81.7, 98.6)	97.6 (94.4, 99.2)
Secondary	F. Q8 (b) (6) Ask a doctor before use: if you have or ever had any cancer	Reviewers	84.9 (81.4, 88.0)	87.8 (83.9, 91.0)	77.0 (68.7, 84.0)	78.4 (67.3, 87.1)	84.6 (74.7, 91.8)	86.5 (82.3, 90.0)	87.2 (82.2, 91.3)	84.4 (70.5, 93.5)	82.4 (76.5, 87.4)
Secondary	G. Q7 (b) (6) Ask a doctor or pharmacist before use if: you are taking a prescription drug for seizures, tuberculosis, HIV/AIDS, pulmonary hypertension	Reviewers	78.0 (74.0, 81.6)	79.2 (74.6, 83.3)	74.6 (66.1, 81.9)	68.9 (57.1, 79.2)	78.2 (67.4, 86.8)	80.0 (75.2, 84.2)	82.4 (76.8, 87.1)	64.4 (48.8, 78.1)	76.1 (69.7, 81.8)
Secondary	H. Q12 (b) (6) Ask a doctor or pharmacist before use if: you are taking a supplement containing St. John's Wort (an herbal ingredient)	Reviewers	82.6 (78.9, 85.9)	83.5 (79.2, 87.2)	80.2 (72.1, 86.7)	78.4 (67.3, 87.1)	79.5 (68.8, 87.8)	84.3 (79.9, 88.1)	84.6 (79.2, 89.0)	73.3 (58.1, 85.4)	82.4 (76.5, 87.4)

Endpoint Type	Endpoint Name	Reviewer or Applicant Reported	Total N=477	NL N=351	LL N=126	Age 11-14 N=74	Age 15-17 N=78	Age 18-50 N=325	History of HBC/OC N=227	History of HBC/No OC N=45	No History of HBC N=205
Secondary	I. Q10 (b) (6) Ask a doctor or pharmacist before use if: you have used an emergency contraceptive (morning after pill) containing ulipristal acetate in the past 5 days	Applicant & reviewers	81.6 (77.8, 84.9)	84.6 (80.4, 88.2)	73.0 (64.4, 80.5)	68.9 (57.1, 79.2)	79.5 (68.8, 87.8)	84.9 (80.6, 88.6)	85.0 (79.7, 89.4)	77.8 (62.9, 88.8)	78.5 (72.3, 84.0)

Endpoint Type	Endpoint Name	Reviewer or Applicant Reported	Total N=477	NL N=351	LL N=126	Age 11-14 N=74	Age 15-17 N=78	Age 18-50 N=325	History of HBC/OC N=227	History of HBC/No OC N=45	No History of HBC N=205
Secondary	J. Q11 (b) (6) When using this product: you are likely to experience changes in your menstrual periods, such as irregular periods, spotting or bleeding between your periods, or you may stop having periods	Reviewers	91.6 (88.8, 93.9)	93.5 (90.3, 95.8)	86.5 (79.3, 91.9)	87.8 (78.2, 94.3)	91.0 (82.4, 96.3)	92.6 (89.2, 95.2)	93.0 (88.8, 95.9)	95.6 (84.9, 99.5)	89.3 (84.2, 93.2)
Secondary	K. Q18 (b) (6) When using this product: you may experience headaches, dizziness, nausea, increased appetite, abdominal pain, cramps or bloating	Applicant & reviewers	94.1 (91.6, 96.1)	95.2 (92.4, 97.2)	91.3 (84.9, 95.6)	89.2 (79.8, 95.2)	94.9 (87.4, 98.6)	95.1 (92.1, 97.2)	94.7 (90.9, 97.2)	86.7 (73.2, 94.9)	95.1 (91.2, 97.6)
Secondary	L. Q14 and Q14a (b) (6)) When using this product talk to a doctor (but continue taking every day) if: you have repeated vaginal bleeding brought on by sex	Reviewers	93.7 (91.1, 95.7)	96.6 (94.1, 98.2)	85.7 (78.4, 91.3)	85.1 (75.0, 92.3)	92.3 (84.0, 97.1)	96.0 (93.3, 97.9)	96.9 (93.8, 98.8)	95.6 (84.9, 99.5)	89.8 (84.8, 93.6)
Secondary	M. Q19 and Q19a (b) (6) When using this product talk to a doctor (but continue taking every day) if: you start having periods that last more than 8 days or are unusually heavy	Reviewers	91.8 (89.0, 94.1)	93.5 (90.3, 95.8)	87.3 (80.2, 92.6)	86.5 (76.6, 93.3)	93.6 (85.7, 97.9)	92.6 (89.2, 95.2)	94.3 (90.4, 96.9)	93.3 (81.7, 98.6)	88.8 (83.6, 92.8)

Endpoint Type	Endpoint Name	Reviewer or Applicant Reported	Total N=477	NL N=351	LL N=126	Age 11-14 N=74	Age 15-17 N=78	Age 18-50 N=325	History of HBC/OC N=227	History of HBC/No OC N=45	No History of HBC N=205
Secondary	N. Q21 and Q21a (b) (6) When using this product talk to a doctor (but continue taking every day) if: you start having migraines with aura (headaches that start with changes in vision) or your migraine headaches get worse	Reviewers	92.7 (89.9, 94.8)	95.2 (92.4, 97.2)	85.7 (78.4, 91.3)	86.5 (76.6, 93.3)	96.2 (89.2, 99.2)	93.2 (89.9, 95.7)	95.2 (91.5, 97.6)	84.4 (70.5, 93.5)	91.7 (87.1, 95.1)
Secondary	O. Q25 (b) (6) When using this product take a pregnancy test or talk to a doctor if: your period is late after missing any tablets in the last month	Applicant & reviewers	82.8 (79.1, 86.1)	86.6 (82.6, 90.0)	72.2 (63.5, 79.8)	70.3 (58.5, 80.3)	85.9 (76.2, 92.7)	84.9 (80.6, 88.6)	87.7 (82.7, 91.6)	77.8 (62.9, 88.8)	78.5 (72.3, 84.0)
Secondary	P. Q24 (b) (6) When using this product take a pregnancy test or talk to a doctor if: you have not had a period for 2 months or think you may be pregnant	Applicant & reviewers	92.9 (90.2, 95.0)	94.0 (91.0, 96.3)	89.7 (83.0, 94.4)	89.2 (79.8, 95.2)	89.7 (80.8, 95.5)	94.5 (91.4, 96.7)	96.9 (93.7, 98.8)	88.9 (75.9, 96.3)	89.3 (84.2, 93.2)
Secondary	Q. Q20 (b) (6) Stop use and ask a doctor if: you become pregnant	Reviewers	97.3 (95.4, 98.5)	98.0 (95.9, 99.2)	95.2 (89.9, 98.2)	93.2 (84.9, 97.8)	98.7 (93.1, 100.0)	97.9 (95.6, 99.1)	97.4 (94.3, 99.0)	97.8 (88.2, 99.9)	97.1 (93.7, 98.9)
Secondary	R. Q30 (b) (6) Directions: never skip your daily tablet	Applicant & reviewers	92.7 (89.9, 94.8)	94.0 (91.0, 96.3)	88.9 (82.1, 93.8)	87.8 (78.2, 94.3)	92.3 (84.0, 97.1)	93.8 (90.7, 96.2)	93.8 (89.9, 96.6)	86.7 (73.2, 94.9)	92.7 (88.2, 95.8)
Secondary	S. Q28 (b) (6) Other information: as with any birth control method, this product does not prevent pregnancy all the time	Applicant & reviewers	91.6 (88.8, 93.9)	94.3 (91.3, 96.5)	84.1 (76.6, 90.0)	83.8 (73.4, 91.3)	93.6 (85.7, 97.9)	92.9 (89.6, 95.5)	95.6 (92.0, 97.9)	91.1 (78.8, 97.5)	87.3 (82.0, 91.5)
Other	Other (b) (6)) Ask a doctor before use: if you have liver problems	Applicant & reviewers	93.7 (91.1, 95.7)	95.2 (92.4, 97.2)	89.7 (83.0, 94.4)	87.8 (78.2, 94.3)	93.6 (85.7, 97.9)	95.1 (92.1, 97.2)	95.2 (91.5, 97.6)	93.3 (81.7, 98.6)	92.2 (87.6, 95.5)

Source: FDA reviewer's table with the LCS study data submitted by the Applicant.
Abbreviations: DFL, drug facts label; FD&C, Food, Drugs and Cosmetics Act; HBC, hormonal birth control; IUD, intrauterine device; LL, limited literacy; NL, normal literacy

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Table 12. DFL Label Comprehension Study: Selected Incorrect Verbatim Responses for "Do Not Use if You Have or Ever Had Breast Cancer"

Participant ID	Verbatim Response
(b) (6)	I remember seeing that somewhere too. Ask your doctor before you use it. I don't know if it's okay or it's not okay, but check with your doctor first.
(b) (6)	It's not okay if you--it says that ask a doctor before use it if you have or if you have any cancer.
(b) (6)	I know it's not okay. I need to look. Oh, here. Ask a doctor before using if you have any cancer.
(b) (6)	PARTICIPANT: No, it says here if you've ever had any type of cancer ask a doctor before use. INTERVIEWER: And I want to just clarify your answer to make sure I was correct here. You said it's not okay.
(b) (6)	PARTICIPANT: I would say it's okay. I don't see any--oh, no, no, no. It says ask a doctor before use if you have or ever had any cancer, so it is not okay.
(b) (6)	I thought I remembered it saying do not take if you have cancer. Yes, they should ask a doctor if you have or have ever had any cancer.
(b) (6)	PARTICIPANT: Not okay. INTERVIEWER: What, if anything, does the label say about that? PARTICIPANT: So it says, Ask a doctor before use if you have or have had any cancer.
(b) (6)	PARTICIPANT: I saw something somewhere. It wasn't okay to take. INTERVIEWER: What, if anything, does the label say about that? PARTICIPANT: Yes. Ask a doctor if-- or if you have ever had any cancer.
(b) (6)	PARTICIPANT: No. INTERVIEWER: And does the label say anything about that? PARTICIPANT: Yes. It says in bold underneath, Ask a doctor before use if you have or ever had any cancer.
(b) (6)	PARTICIPANT: It says, Ask a doctor before you use it. So no, do not use. INTERVIEWER: And what, if anything, does the label say about that? PARTICIPANT: Do not use if you have or ever had breast cancer.
(b) (6)	She shouldn't. Ask a doctor first, but it does say, do not use if you have or ever had breast cancer.
(b) (6)	PARTICIPANT: According to the label, you shouldn't be using it if you have or had any cancer. INTERVIEWER: Okay. PARTICIPANT: Or ask your doctor about it.
(b) (6)	No, I'm just trying to find where that was at that I read that. Yes, it says, Ask a doctor if you have ever had any cancer. Or it just says to talk to your doctor about it first anyway.
(b) (6)	PARTICIPANT: Not okay. INTERVIEWER: What, if anything, does the label say about that? PARTICIPANT: Ask a doctor before use if you have or ever had any cancer.
(b) (6)	PARTICIPANT: It says, Do not use. INTERVIEWER: And what else, if anything, does the label say about that? PARTICIPANT: It says, Ask a doctor before use if you have or ever had any cancer.
(b) (6)	It is not okay. She has to talk to her doctor first if you've ever had any cancer.
(b) (6)	PARTICIPANT: Not okay. INTERVIEWER: What, if anything, does the label say about that? PARTICIPANT: Ask a doctor before use if you have or ever had any cancer.
(b) (6)	PARTICIPANT: No, it's not okay for her to use [it?]. INTERVIEWER: What, if anything, does the label say about that? PARTICIPANT: It said that people who have cancer should not be using it. And where did it
(b) (6)	PARTICIPANT: Not okay. INTERVIEWER: What, if anything, does the label say about that? PARTICIPANT: Ask a doctor before use if you have or ever had any cancer.

Source: Verbatim responses drawn from dataset horiz.xpt for the combined LCS and targeted breast cancer self-selection study in the Applicant's NDA submission.
Participants' selected verbatim responses to the question: "(b) (6) had breast cancer. According to the label, is it OK or not OK for her to use Opill? What, if anything, does the label say about that"?
Abbreviations: DFL, drug facts label; ID, identifier

Table 13. Label DFL Comprehension Study of DFL: Unexplained Vaginal Bleeding Selected Incorrect Verbatim Responses

Participant ID	Verbatim Response
(b) (6)	So I think it talks about in a few different places. So it says when using this product, you are likely to experience changes in your menstrual periods, such as irregular periods, spotting, or bleeding between your periods, or you may stop having periods. And then lower down, it says if you start having periods that last more than eight days or are unusually heavy, talk to a doctor. If you have repeated vaginal bleeding, okay. So talk to a doctor if you have repeated vaginal bleeding.
(b) (6)	I believe she's supposed to talk to her doctor, but I think it's still okay for her to take it. But let me just make sure. Yes, talk to your doctor but continue taking every day if you have repeated vaginal bleeding brought on by sex.
(b) (6)	I don't see anything on the label regarding that, so I'm not sure about this. Maybe she should see her doctor. I would say that.
(b) (6)	I remember it saying something about spotting in between periods. It says talk to your doctor if you start having periods that last more than eight days or unusually heavy periods. And this product can experience irregular periods, spotting, or bleeding between your periods, or you may stop having periods.
(b) (6)	So it does say, when using this product, talk to a doctor but continue taking it every day if you had repeated vaginal bleeding brought on by sex.
(b) (6)	Continue taking the pill every day.
(b) (6)	It says talk to a doctor, but you can continue to take every day.
(b) (6)	Talk to your doctor but continue taking every day. If you have repeated vaginal bleeding, if you start having periods.
(b) (6)	It says that she can start taking Opill and that to prevent it, to just keep taking the product since it is likely that she's going to experience changes in her menstrual period but if anything seems out of sorts, to see a doctor.
(b) (6)	Talk to a doctor, but you can take it.
(b) (6)	Talk to a doctor, but you can take it.
(b) (6)	Even though she didn't talk to a doctor, it's best for her to talk to a doctor, even if she is bleeding in between and to take it every day.
(b) (6)	It says to talk to a doctor, and it says that it does cause irregular – or you should just seek medical help.
(b) (6)	It says talk to a doctor if you have repeated vaginal bleeding brought on by sex. That's the only thing I see here.
(b) (6)	Okay. The label says that if you are experiencing vaginal bleeding between periods to talk to a doctor.

Source: Verbatim responses drawn from the dataset horiz.xpt for the combined LCS and targeted breast cancer self-selection in the Applicant's NDA submission.
Participants' selected verbatim responses to the question: (b) (6) has vaginal bleeding between her periods and has never talked to her doctor about it. She is thinking about starting Opill. What if anything does the label say about that?"
Abbreviations: DFL, drug facts label; ID, identifier

5.11 Label Comprehension Study of Consumer Information Leaflet: Tables

Table 14. Label Comprehension Study of CIL: Demographics

Demographic Characteristic	All[1] (N=551)
Gender	
Female	479 (86.9%)
Male	72 (13.1%)
Refused	0 (0.0%)
Hispanic or Latino	
Yes	118 (21.4%)
No	433 (78.6%)
Refused	0 (0.0%)

Demographic Characteristic	All[1] (N=551)
Race	
White	339 (61.5%)
Black or African American	135 (24.5%)
Asian	6 (1.1%)
Native Hawaiian or Other Pacific Islander	1 (0.2%)
American Indian or Alaska Native	2 (0.4%)
Refused	0 (0.0%)
Other	68 (12.3%)
Education level	
Eighth grade or less	60 (10.9%)
Some high school	118 (21.4%)
High school graduate, GED, or certificate	70 (12.7%)
Some college or technical school	139 (25.2%)
College graduate	110 (20.0%)
Postgraduate degree	54 (9.8%)
Refused	0 (0.0%)
Don't know	0 (0.0%)
Age/gender category	
Female aged 11-17	151 (27.4%)
Female aged 18-24	124 (22.5%)
Female aged 25-45	129 (23.4%)
Female aged 46+	75 (13.6%)
Male aged 11-17	15 (2.7%)
Male aged 18+	57 (10.3%)
None of these	0 (0.0%)
Annual household income	
Less than $25,000	98 (17.8%)
$25,000-$34,999	78 (14.2%)
$35,000-$49,999	97 (17.6%)
$50,000-$74,999	108 (19.6%)
$75,000-$99,999	80 (14.5%)
$100,000-$149,999	55 (10.0%)
$150,000 or more	25 (4.5%)
Refused	10 (1.8%)
Hormone contraceptive use in females[2]	N=479
Never used hormonal contraceptives	211 (38.3%)
Past hormonal contraceptive use	160 (29.0%)
Current hormonal contraceptive use	108 (19.6%)
Any hormonal contraceptive use[3]	268 (48.6%)

Source: Applicant's Study Report.

[1] Participant (b) (6) completed the comprehension interview and refused the REALM-Teen Literacy assessment.

[2] Males were not asked questions about hormonal contraceptive use.

[3] Sum of participants with past or current hormonal contraceptive use.

Abbreviations: CIL, consumer information leaflet; GED, general educational development; n, number of participants

Table 15. Label Comprehension Study of CIL: Endpoint Results

No.	Endpoint Name	Reviewer-Reported or Applicant Reported	Total N=551	Literacy		Age		HBC Use	
				NL N=414	LL N=136	Women 18+ N=328	Women 11-17 N=151	Current or Past Use of HBC N=268	Never Used HBC N=211
1	**Q18.** (b) (6) What is Pill®? Opill® is NOT an emergency contraceptive.	Applicant/reviewer	85.1 (81.9, 88.0)	89.1 (85.7, 92.0)	73.5 (65.3, 80.7)	85.4 (81.9, 88.4)	80.8 (73.6, 86.7)	90.7 (86.5, 93.9)	78.7 (72.5, 84.0)
2	**Q16.** (b) (6) How to take Opill®: To start using Opill®: If you are switching from another birth control pill, vaginal ring, or patch, start taking Opill® the day after you stop the other method.	Applicant/reviewer	81.1 (77.6, 84.3)	86.2 (82.5, 89.4)	66.2 (57.6, 74.1)	82.5 (78.8, 85.8)	74.2 (66.4, 80.9)	87.7 (83.1, 91.4)	75.8 (69.5, 81.4)
3	**Q17.** (b) (6) How to take Opill®: What if I am late taking my pill? Less than 3 hours late: Don't worry. Take 1 pill immediately	Reviewer	94.7 (92.5, 96.5)	95.9 (93.5, 97.6)	91.9 (86.0, 95.9)	95.4 (92.6, 97.4)	93.4 (88.2, 96.8)	96.6 (93.7, 98.5)	92.4 (88.0, 95.6)
4	**Q17** (b) (6) How to take Opill®: What if I am late taking my pill? Less than 3 hours late: Don't worry. …..then go back to taking your pill at your usual time the following day.	Applicant/reviewer	95.3 (93.2, 96.9)	96.6 (94.4, 98.1)	91.9 (86.0, 95.9)	95.7 (92.9, 97.6)	96.0 (91.6, 98.5)	97.0 (94.2, 98.7)	94.3 (90.3, 97.0)
5	**Q19.** (b) (6) What changes in my menstrual period are normal while using Opill®? Continue taking Opill® exactly as directed even if you have the following changes in your periods: Your periods may be less or more frequent, shorter or longer, lighter or heavier than before you started Opill®. You may also have some spotting or bleeding between periods.	Applicant/reviewer	96.4 (94.4, 97.8)	98.1 (96.2, 99.2)	91.9 (86.0, 95.9)	96.7 (94.6, 98.1)	96.7 (92.4, 98.9)	97.0 (94.2, 98.7)	96.2 (92.7, 98.3)

No.	Endpoint Name	Reviewer-Reported or Applicant Reported	Total N=551	Literacy		Age		HBC Use	
				NL N=414	LL N=136	Women 18+ N=328	Women 11-17 N=151	Current or Past Use of HBC N=268	Never Used HBC N=211
6	**Q21** (b) (6) What changes in my menstrual period are normal while using Opill®? Continue taking Opill® exactly as directed even if you have the following changes in your periods: Some women stop having periods while taking Opill®. If you haven't had a period in 2 months, take a pregnancy test or talk to a doctor.	Reviewer	85.3 (82.1, 88.2)	89.9 (86.5, 92.6)	71.3 (63.0, 78.8)	88.7 (84.8, 91.9)	80.8 (73.6, 86.7)	90.3 (86.1, 93.6)	81.0 (75.1, 86.1)
7	**Q20.** (b) (6) What changes to my menstrual period are NOT expected when using Opill®? Talk to a doctor while continuing to take this product every day even if you experience any of the following: You repeatedly have bleeding that is brought on by sex.	Reviewer	82.4 (79.0, 85.5)	86.5 (82.8, 89.6)	70.6 (62.2, 78.1)	83.5 (79.1, 87.4)	80.1 (72.9, 86.2)	85.5 (80.7, 89.4)	78.7 (72.5, 84.0)
8	**22.** (b) (6) What changes to my menstrual period are NOT expected when using Opill®? Talk to a doctor while continuing to take this product every day even if you experience any of the following: Your menstrual period lasts more than 8 days or is unusually heavy.	Reviewer	78.8 (75.1, 82.1)	81.4 (77.3, 85.0)	71.3 (63.0, 78.8)	80.5 (75.8, 84.6)	72.9 (65.0, 79.8)	83.6 (78.6, 87.8)	71.1 (64.5, 77.1)
9	**24.** (b) (6) Other questions: How effective is Opill®? As with any birth control method, Opill® does not prevent pregnancy all the time.	Reviewer	92.4 (89.8, 94.5)	96.1 (93.8, 97.8)	81.6 (74.1, 87.7)	93.3 (90.0, 95.8)	89.4 (83.4, 93.8)	95.5 (92.3, 97.7)	87.7 (82.5, 91.8)

No.	Endpoint Name	Reviewer-Reported or Applicant Reported	Total N=551	Literacy		Age		HBC Use	
				NL N=414	LL N=136	Women 18+ N=328	Women 11-17 N=151	Current or Past Use of HBC N=268	Never Used HBC N=211
10	**27.** (b) (6) Other questions: If you decide you want to become pregnant, simply stop taking Opill®. Opill® will not delay your ability to get pregnant.	Applicant/reviewer	98.2 (96.7, 99.1)	99.0 (97.5, 99.7)	96.3 (9.6, 98.8)	97.9 (96.2, 99.0)	98.0 (94.3, 99.6)	98.9 (96.8, 99.8)	96.7 (93.3, 98.7)
11	**26.** (b) (6) Other questions: Is it OK to use Opill® if I'm breastfeeding? Yes. Opill® is safe and effective in breastfeeding women.	Applicant/reviewer	96.4 (94.4, 97.8)	97.3 (95.3, 98.7)	93.4 (87.8, 96.9)	95.8 (93.6, 97.4)	96.7 (92.4, 98.9)	96.6 (93.7, 98.5)	94.8 (90.9, 97.4)
12	**23.** (b) (6) "What if I have taken an emergency contraceptive before starting Opill?... Also, use a condom (or another barrier method) every time you have sex until your next period."	Applicant	80.4 (76.8, 83.6)	86.5 (82.8, 89.6)	62.5 (53.8, 70.6)	86.9 (82.7, 90.3)	65.6 (57.4, 73.1)	91.8 (87.8, 94.8)	65.4 (58.6, 71.8)

Source: FDA reviewer's table with the LCS study data submitted by the Applicant.
Abbreviations: HBC, hormonal birth control; LL, limited literacy; NL, normal literacy

5.12 Targeted Self-Selection Study: Tables

Table 16. Targeted Self-Selection Study: Demographics

Demographic Characteristic	Self-Selection Population (N=206)
Age distribution	
Mean (SD)	44.2 (4.7)
Median	45
Range (min, max)	(31, 50)
Age group (years)	
11-14	0 (0.0%)
15-17	0 (0.0%)
18-24	0 (0.0%)
25-45	109 (52.9%)
46+	97 (47.1%)
Adult education level	
Eighth grade or less	0 (0.0%)
Some high school	1 (0.5%)
High school graduate or GED	16 (7.8%)
Some college or technical school	30 (14.6%)
College graduate	96 (46.6%)
Post-graduate college degree	64 (30.6%)
Refused	0 (0.0%)
Adolescent education level	
Seventh grade or less	0 (0.0%)
Eighth grade	0 (0.0%)
Ninth grade (freshman in high school)	0 (0.0%)
Tenth grade (sophomore in high school)	0 (0.0%)
Eleventh grade (junior in high school)	0 (0.0%)
Twelfth grade (senior in high school)	0 (0.0%)
High school graduate, GED, or certificate	0 (0.0%)
Some college or technical school	0 (0.0%)
College graduate	0 (0.0%)
Refused	0 (0.0%)
Ethnicity	
Hispanic or Latinx	23 (11.2%)
Not Hispanic or Latinx	183 (88.8%)
Refused	0 (0.0%)
Race[1]	
White	163 (79.1%)
Black or African American	35 (17.0%)
Asian	5 (2.4%)
Native Hawaiian or Other Pacific Islander	1 (0.5%)
American Indian or Alaska Native	3 (1.5%)
Other	5 (2.4%)
Refused	0 (0.0%)
Household income	
Less than $25,000	3 (1.5%)
$25,001-$50,000	23 (11.2%)
$50,001-$75,000	44 (21.4%)
$75,001-$100,000	37 (18.0%)
$100,001-$150,000	57 (27.7%)
More than $150,000	40 (19.4%)
Refused	2 (1.0%)

Demographic Characteristic	Self-Selection Population (N=206)
Health literacy[2]	
Normal	196 (95.1%)
Low	10 (4.9%)
Refused REALM/unknown health literacy	0 (0.0%)
History of HBC use	
History of HBC use and OC use	166 (80.6%)
History of HBC use but no OC use	22 (10.7%)
No history of HBC use	18 (8.7%)

Source: Applicant's Study Report.

[1] Answers below are not mutually exclusive.

[2] Normal: Participants scoring ≥61 on the REALM or REALM-Teen test. Low: Participants scoring ≤60 on the REALM or REALM Teen test.

Abbreviations: GED, general educational development; HBC, hormonal birth control; OC, oral contraceptive; REALM, Rapid Estimate of Adult Literacy in Medicine

Table 17. Targeted Breast Cancer Study: Summary of Verbatim Response for Six Incorrect Selectors

Participant number	Age	Literacy	Summary Narrative
(b) (6)	42	NL	Participant reported that she had been diagnosed with a hormone-sensitive breast cancer approximately 10 months ago, received her last treatment approximately 6 months ago, and stated that she is currently in remission. The participant reported that the product was okay for her to use because "it's for people who ever had breast cancer". Additionally, the participant reported that she would purchase the product because the cost of the product is low and there was nothing on the label indicating that she should not use Opill.
(b) (6)	47	NL	Participant reported that she had been diagnosed with a hormone-sensitive breast cancer approximately 16 months ago, received her last treatment approximately 10 months ago, and stated that she is currently in remission. The participant stated that she could use the product but wasn't sure how much estrogen was in the birth control so she would need to talk to her doctor about it. She also indicated that she would purchase the product because of the low cost and there was nothing on the label indicating that she should not use Opill.
(b) (6)	49	NL	Participant reported that she had been diagnosed with breast cancer (not hormone sensitive) approximately 3 years ago, received her last treatment approximately 1.5 years ago, and stated that she is currently in remission. The participant stated that she could use the product because it was a pill she could take daily. However, when asked if she would purchase the product, the participant stated that she would purchase it, but she has an IUD and doesn't need to take any other type of birth control.
(b) (6)	46	NL	Participant reported that she had been diagnosed with a hormone-sensitive breast cancer approximately one month ago and was planning to start treatments in approximately one week. The participant states that she could use the product because she did not have a contraindication such as allergies or prescriptions for seizures, tuberculosis, or St. John's Wort. She also indicated that she would purchase the product because of the low cost to prevent pregnancy and there was nothing on the label indicating that she should not use Opill.
(b) (6)	49	NL	Participant reported that she had been diagnosed with breast cancer (not hormone sensitive) approximately seven years ago and stated that she is currently in remission. The participants stated that she could use the product because there were no indications that it could affect her health.
(b) (6)	45	NL	Participant reported that she had been diagnosed with breast cancer (she was unsure if it was hormone-sensitive) approximately 18 years ago and stated she is currently in remission. She stated that she could use the product because of her health history, and it is a daily oral contraceptive.

Source: Table 10 of Applicant Study Report
Abbreviations: NL, normal literacy

5.13 Self-Selection in Actual Use Study: Tables

5.13.1 Demographics

Table 18. Self-Selection in Actual Use Study: Demographics

Demographic Characteristic	Self-Selection Population (N=1772)
Sex	
Female	1765 (99.6%)
Male	7 (0.4%)
Race	
American Indian or Alaska Native	53 (3.0%)
Asian	106 (6.0%)
Black or African American	534 (30.1%)
Native Hawaiian or Other Pacific Islander	25 (1.4%)
White	1057 (59.7%)
Other	105 (5.9%)
Refused	16 (0.9%)
Missing (participant did not pass screening)	NA
Ethnicity	
Hispanic or Latino/Latina	306 (17.3%)
Not Hispanic or Latino/Latina	1464 (82.6%)
Refused	2 (0.1%)
Missing (participant did not pass screening)	NA
Age group/gender category	
Female age 10 or younger	0 (0.0%)
Female age 11-14	88 (5.0%)
Female age 15-17	275 (15.5%)
Female age 18-19	133 (7.5%)
Female age 20-24	412 (23.3%)
Female age 25-34	518 (29.2%)
Female age 35+	339 (19.1%)
Female age 35-45	283 (16.0%)
Female age 46-55	41 (2.3%)
Female aged 56+	15 (0.8%)
Male	7 (0.4%)
Refused	0 (0.0%)
Age distribution	
Mean	26.2
SD	9.19
Median	24.0
Range	12, 68
Female participants aged 11-19 by age	
Age 11	0 (0.0%)
Age 12	4 (0.2%)
Age 13	36 (2.0%)
Age 14	48 (2.7%)
Age 15	44 (2.5%)
Age 16	79 (4.5%)
Age 17	152 (8.6%)
Age 18	67 (3.8%)
Age 19	66 (3.7%)
Health literacy	
Normal	1539 (86.9%)
Low	226 (12.8%)
Refused	7 (0.4%)
Missing (participant did not pass screening)	NA

Demographic Characteristic	Self-Selection Population (N=1772)
(Females only) history of HBC use	
History of HBC use	1333 (75.2%)
History of oral contraceptive use	1148 (64.8%)
No history of oral contraceptive use	185 (10.4%)
No history of HBC use	439 (24.8%)
Missing (participant did not pass screening)	NA
Education Level (18+)	
Eighth grade or less	5 (0.3%)
Some high school	53 (3.0%)
High school graduate, GED, or certificate	304 (17.2%)
Some college or technical school	571 (32.2%)
College graduate	384 (21.7%)
Postgraduate degree	89 (5.0%)
Refused	0 (0.0%)
Missing (participant did not pass screening)	NA
Education level (11-17)	
Seventh grade or less	37 (2.1%)
Eighth grade	47 (2.7%)
Ninth grade	54 (3.0%)
Tenth grade	83 (4.7%)
Eleventh grade	109 (6.2%)
Twelfth grade	14 (0.8%)
High school graduate, GED, or certificate	16 (0.9%)
Some college or technical school	6 (0.3%)
College graduate	0 (0.0%)
Refused	4 (0.2%)
Missing (participant did not pass screening)	NA
Estimated annual household income	
Less than $25,000	540 (30.5%)
$25,001-$50,000	551 (31.1%)
$50,001-$75,000	263 (14.8%)
$75,001-$100,000	127 (7.2%)
$100,001-$150,000	114 (6.4%)
More than $150,000	53 (3.0%)
Don’t know	120 (6.8%)
Refused	4 (0.2%)
Missing (participant did not pass screening)	NA

Source: Applicant’s Study Report.
Abbreviations: GED, General educational development; HBC, hormonal birth control; N, number of subjects; NA, not applicable; SD, standard deviation

5.13.2 Subgroups of Cancer, Liver Disease, and Unexplained Vaginal Bleeding

Table 19. Self-Selection in Actual Use Study: Cancer Subgroup (n=14)

Participant ID	Type of Cancer	Initial Selection Decision	Said Yes to Purchase?	Applicant's Final Categorization of Selection	FDA's Final Categorization of Selection	Applicant's initial Decision on Appropriate to Use	Applicant's Final Decision on Appropriate to Use	FDA Medical Assessment on Appropriate to Use, Cell Re/classification
(b) (6) LL	Breast cancer about 4 years ago and abnormal uterine bleeding	Selector It doesn't seem to have very many warning signs	Y	Selector	Selector	Not appropriate Cell B	Not appropriate Cell B	Not appropriate Cell B
(b) (6) LL	Cancer type unclear; she referred to it as "venereal"	Selector My youngest daughter is 26 and right now I do not need any more babies	N due to cost	Selector	Selector	Not appropriate Cell B	Not appropriate Cell B	Not appropriate Cell B
(b) (6) NL	Thyroid cancer – "currently cured"	Selector Something to try	Y	Selector	Selector	Not appropriate Cell B	Appropriate Cell A	Not Appropriate Cell B
(b) (6) NL	History of skin Cancer – "cured"	Selector Because you don't have to wait to start the medication until you are on your period.	Y	Selector	Selector	Not appropriate Cell B	Appropriate Cell A	Not appropriate Cell B

Participant ID	Type of Cancer	Initial Selection Decision	Said Yes to Purchase?	Applicant's Final Categorization of Selection	FDA's Final Categorization of Selection	Applicant's initial Decision on Appropriate to Use	Applicant's Final Decision on Appropriate to Use	FDA Medical Assessment on Appropriate to Use, Cell Re/classification
(b) (6) NL	Stage 3 metastatic melanoma in remission	Selector There is no estrogen in it, it seems pretty low dose of norgestrel, same precaution that I have taken in past birth control	Y	Selector	Selector	Not appropriate Cell B	Appropriate Cell A	Not appropriate Cell B
(b) (6) NL	History of cervical dysplasia	Selector I'm coming off the Depo- shot now and in need of new birth control.	Y	Selector	Selector	Not appropriate Cell B Check	Appropriate Cell A	Appropriate Cell A
(b) (6) NL	Thyroid and non-Hodgkin's lymphoma	Wants to talk with Dr. to make sure it doesn't interfere with other meds	N	Non-selector	Selector	Not appropriate Cell D Check	Not appropriate Cell D	Not appropriate Cell B
(b) (6) NL	Cervical cancer and basal cell	Non-selector	N (due to hypertension)	Non-selector	Non-selector	Not appropriate Cell D	Not appropriate Cell D	Not appropriate Cell D
(b) (6) NL	Breast cancer	Would talk to a pharmacist due to health issues	N	Non-selector	Selector	Not appropriate Cell D	Not appropriate Cell D	Not appropriate Cell B

Participant ID	Type of Cancer	Initial Selection Decision	Said Yes to Purchase?	Applicant's Final Categorization of Selection	FDA's Final Categorization of Selection	Applicant's initial Decision on Appropriate to Use	Applicant's Final Decision on Appropriate to Use	FDA Medical Assessment on Appropriate to Use, Cell Re/classification
(b) (6) NL	Cervical cancer	Non-selector Has had cancer and package says not to use if you have had cancer	N	Non-selector	Non-selector	Not appropriate Cell D	Not appropriate Cell D	Not appropriate Cell D
(b) (6) NL	Colon cancer	Selector	N (she was menopausal but would purchase for granddaughter (age 62)	Non-selector	Selector	Not appropriate Cell D	Not appropriate Cell D	Not appropriate Cell B
(b) (6) NL	Skin cancer	Selector Similar to what I already take	N	Already using a BC method and don't want to change Non-selector	Selector	Not appropriate Cell D	Not appropriate Cell D	Not appropriate Cell B
(b) (6) NL	Thyroid cancer	Selector Don't have to worry about BP being elevated	D/K	Currently on ortho tri-cyclen and don't want to have break-through bleeding starting something new Non-selector	Selector	Not appropriate Cell D	Not appropriate Cell D	Not appropriate Cell B
(b) (6) LL Adolescent	Thyroid cancer	Non-selector	N	Non-selector	Non-selector	Not appropriate Cell D	Not appropriate Cell D	Not appropriate Cell D

Source: Reviewer, based on the ACCESS dataset adsl.xpt in the Applicant's NDA submission and reviewer reclassification.
Abbreviations: BC, birth control; BP, blood pressure; D/K, don't know; FDA, Food and Drug Administration; ID, identifier; LL, limited literacy; N, no; NL, normal literacy; Y, yes

Table 20. Self-Selection in Actual Use Study: Liver Disease Subgroup (n=7)

Participant ID	Type of Liver Problem(s)	Initial Selection Decision	Said Yes to Purchase?	Applicant's Final Categorization of Selection	FDA's Final Categorization of Selection	Applicant's Initial Decision on Appropriate to Use	Applicant's Final Decision on Appropriate to Use	FDA Medical Assessment on Appropriate to Use, Cell Re/Classification
(b) (6) NL	Fatty liver disease – lost 45 pounds and Dr. said I was OK	Selector	Y	Selector	Selector	Not appropriate	Acceptable	Acceptable Cell A
(b) (6) NL	Fatty liver disease/obesity	Selector	Y	Selector	Selector	Not appropriate	Acceptable	Acceptable Cell A
(b) (6) NL	Hepatitis, acute liver disease. Used Epclusa, had a F0 fibrosis score – it worked	Selector	N, want to AAD because I've had problems with IUD and the pill may be a better option. Want to make sure I'm not pregnant	Selector	Selector (did not mention medical condition for AAD)	Appropriate	Acceptable	Not appropriate Cell B
(b) (6) NL	Fatty liver disease, needs to lose weight	Selector – it prevents pregnancy and I need it	Y	Selector	Selector	Not appropriate	Acceptable	Acceptable
(b) (6) NL	-	-	N, already using BC and doesn't want to change	Non-selector	Selector	Not appropriate	Not appropriate	Not appropriate Cell B
(b) (6) NL	-		AAD to see if this is more effective than current BC	Non-selector	Selector	Not appropriate	Not appropriate	Not appropriate Cell B
(b) (6)	-		N, don't need BC right now	Non-selector	Selector	Not appropriate	Not appropriate	Not appropriate Cell B

Source: Reviewer, based on the ACCESS dataset adsl.xpt in the Applicant's NDA submission and reviewer reclassification.
Abbreviations: AAD, ask a doctor; BC, birth control; FDA, Food and Drug Administration; ID, identifier; IUD, intrauterine device; N, no; NL, normal literacy; Y, yes

Table 21. Self-Selection in Actual Use Study: Unexplained Vaginal Bleeding Subgroup (n=25)

Participant ID	Vaginal Bleeding	Initial Selection Decision	Said Yes to Purchase?	Applicant's Final Classification of Selection	FDA's Final Classification of Selection	Applicant's Initial Decision on Appropriate to Use	Applicant's Final Decision on Appropriate to Use	FDA Clinical Assessment on Appropriate to Use, Cell Re/classification
(b) (6) NL Adolescent	17-year-old with rare, irregular bleeding	Selector	Y	Selector	Selector	Appropriate	Acceptable	Not appropriate Cell B Not enough info
(b) (6) NL		Selector – I enjoy taking the pill and how it regulates me	N, already using a BC and doesn't want to change	Non-selector	Selector	Not appropriate	Not appropriate	Not appropriate Cell B
(b) (6) NL		Selector	N – would like to AAD	Non-selector	Non-selector	Not appropriate	Not appropriate	Not appropriate Cell D
(b) (6) NL		Selector – It would fit well in my day to day life	N, I would like to talk to a doctor first – how it could work for me -I've had some bad reactions before	Non-selector	Non-selector	Not appropriate	Not appropriate	Not appropriate Cell D
(b) (6) LL Adolescent		Selector	N	Non-selector, already using birth control	Selector	Not appropriate	Not appropriate	Not appropriate Cell B
(b) (6) LL		Selector – I don't take any medicine now	N, would like to talk to a doctor first because periods are irregular and don't want to worsen it	Non-selector	Non-selector	Not appropriate	Not appropriate	Not appropriate Cell D

Participant ID	Vaginal Bleeding	Initial Selection Decision	Said Yes to Purchase?	Applicant's Final Classification of Selection	FDA's Final Classification of Selection	Applicant's Initial Decision on Appropriate to Use	Applicant's Final Decision on Appropriate to Use	FDA Clinical Assessment on Appropriate to Use, Cell Re/classification
(b) (6) NL	Have it 2 months or less, a few times	Selector, it will let me know when my periods will start	Y	Selector	Selector	Appropriate	Appropriate	Not appropriate Cell B Not enough information
(b) (6) NL		Would talk to a doctor about the unexplained vaginal bleeding	N	Non-selector	Non-selector	Not appropriate	Not appropriate	Not appropriate Cell D
(b) (6) NL		AAD about bleeding	N	Non-selector	Non-selector	Not appropriate	Not appropriate	Not appropriate Cell D
(b) (6) LL	Often – 3-8 times/year	Selector – it said you could stop having your period and I've been on mine all month	N, I don't need BC right now	Non-selector	Selector	Appropriate	Appropriate	Not appropriate Cell B Not enough information to evaluate
(b) (6) NL		Selector – none of the DNU applies to me	N – already using BC and don't want to change	Non-selector	Selector	Not appropriate	Not appropriate	Not appropriate Cell B
(b) (6) NL	Irregular periods and history of unexplained vaginal bleeding between periods, "a couple times"	Selector,	Y	Selector	Selector	Not appropriate	Acceptable	Not appropriate Cell B

Participant ID	Vaginal Bleeding	Initial Selection Decision	Said Yes to Purchase?	Applicant's Final Classification of Selection	FDA's Final Classification of Selection	Applicant's Initial Decision on Appropriate to Use	Applicant's Final Decision on Appropriate to Use	FDA Clinical Assessment on Appropriate to Use, Cell Re/classification
(b) (6) NL Adolescent		Selector, because it would be serving its purpose	N, doesn't need BC right now	Non-selector	Selector	Not appropriate	Not appropriate	Not appropriate Cell B
(b) (6) Note: this subj ID also had liver problems NL	40-year-old with 5 years of occasional abnormal uterine bleeding for which she has never seen a doctor	Selector	Y	Selector	Selector	Not appropriate	Acceptable	Not appropriate Cell B
(b) (6) NL	"I've always had spotting – I've never asked my doctor about it because it's normal to me" – usually for one day	Selector	Y	Selector	Selector	Not appropriate	Acceptable	Not appropriate Cell B
(b) (6) NL		Selector - doesn't have estrogen	N – doesn't need BC now	Non-selector	Selector	Not appropriate	Not appropriate	Not appropriate Cell B
(b) (6) NL Adolescent		Selector	N, want to AAD due to pills I take	Non-selector	Non-selector	Not appropriate	Not appropriate	Not appropriate Cell D
(b) (6) NL	44 and cycles are heavy, spotting as well	Would talk to a doctor.	N	Non-selector	Non-selector	Not appropriate	Not appropriate	Not appropriate Cell D

Participant ID	Vaginal Bleeding	Initial Selection Decision	Said Yes to Purchase?	Applicant's Final Classification of Selection	FDA's Final Classification of Selection	Applicant's Initial Decision on Appropriate to Use	Applicant's Final Decision on Appropriate to Use	FDA Clinical Assessment on Appropriate to Use, Cell Re/classification
(b) (6) NL		Selector – I would rather not go to the doctor to get birth control	N – I have an ovarian cyst I need to see a doctor about	Non-selector	Non-selector	Not appropriate	Not appropriate	Not appropriate Cell D
(b) (6) NL	Few days of mid-cycle spotting - contradictory as to how long this has been happening	Selector	Y	Selector	Selector	Not appropriate	Acceptable	Not appropriate Cell B Same as above; unclear if mid-cycle spotting 2 months or less duration was only referring to the current episode
(b) (6) NL Adolescent	Two months or less, a few times	Selector – because it works in 2 days	N, doesn't need BC right now	Non-selector	Selector	Not appropriate	Not appropriate	Not appropriate Cell B
(b) (6) NL		Selector – I don't really look at the label. It looks like it does what it should do	N, already using BC and doesn't want to change	Non-selector	Selector	Not appropriate	Not appropriate	Not appropriate Cell B
(b) (6) NL	Spotting for 3-6 months with every menstrual cycle – but also stated that was normal for her	Selector, no harsh hormones	Y	Selector	Selector	Not appropriate	Acceptable	Not appropriate Cell B

Participant ID	Vaginal Bleeding	Initial Selection Decision	Said Yes to Purchase?	Applicant's Final Classification of Selection	FDA's Final Classification of Selection	Applicant's Initial Decision on Appropriate to Use	Applicant's Final Decision on Appropriate to Use	FDA Clinical Assessment on Appropriate to Use, Cell Re/classification
(b) (6) LL	Irregular bleeding 2-3 times/year I saw my gyn but we discussed my long periods, not my spotting that I had before the study. My long periods were more of a problem	Selector	Y	Selector	Selector	Appropriate	Appropriate	Not appropriate Cell B
(b) (6) LL	Dr. attributed bleeding to Depo-Provera but that was stopped 3-4 years ago and she has had bleeding since then 2-3 times/year	Selector	Y	Selector	Selector	Appropriate	Appropriate	Not appropriate Cell B

Source: Reviewer, based on the ACCESS dataset adsl.xpt in the Applicant's NDA submission and reviewer reclassification.
Abbreviations: AAD, ask a doctor; BC, birth control; FDA, Food and Drug Administration; ID, identifier; LL, limited literacy; N, no; NL, normal literacy; Y, yes
Note: participants (b) (6) and (b) (6) had discussed one type of abnormal vaginal bleeding with their doctors prior to the self-selection interview, but still had other unexplained vaginal bleeding that they did not discuss at that time.

5.13.3 Reviewers' Classification Procedure

Step 1: The Applicant stated in the Response to FDA's information request#51 (submitted February 7, 2023) that "367 Participants who, in response to the initial selection question said the product was okay to use and in response to the purchase question said "No" and were classified as non-selectors." FDA reviewers disagree with this classification. As stated in the FDA Self-Selection Guidance (2013), a selector is anyone who says that the product is appropriate for them to use, given their particular medical conditions. It does not mean that the participant actually chose to use the product. Per the Guidance, purchase decision does not determine the selector category, because there can be many reasons why a participant does not want to purchase a product. Therefore, Reviewers changed the selection decision from "non-selector" to "selector" for the 367 participants, unless they were in the subgroups of participants with cancer (N=14), vaginal bleeding (N=25), or liver problem subgroup (N=7), since these participants were the focus of the reviewers' manual review. As a result, 354 participants were moved from "non-selector" to "selector" (Table 22).

Table 22. Self-Selection Study: Reviewers' Classification Step 1

Self-Selection Population N=1772	Appropriate or Acceptable to Use N=1694	Not Appropriate to Use N=78
Selector (N=1534)	Cell A N=1496	Cell B N=38
Non-selector (N=238)	Cell C N=198	Cell D N=40

Source: FDA reviewer's table
Abbreviation: N, number of subjects

Step 2: The reviewers manually reviewed the selection decisions and appropriate to use classifications for participants in three subgroups of interest: cancer (N=14), vaginal bleeding (N=25), and liver disease (n=7). Note that one participant was in both liver problem and vaginal bleeding subgroups, so in total 45 participants were reviewed. During the manual review, 16 participants' selection decisions were changed from "non-selector" to "selector", and 14 participant's appropriate to use classifications were changed from "appropriate or acceptable to use" to "Not appropriate to Use" (Table 23).

Table 23. Self-Selection Study: Reviewers' Classification Step 2

Self-Selection Population N=1772	Appropriate or Acceptable to Use N=1680	Not Appropriate to Use N=92
Selector (N=1550)	Cell A N=1483	Cell B N=67
Non-selector (N=222)	Cell C N=197	Cell D N=25

Source: FDA reviewer's table
Correct deselection D/(B+D): 25/92 = 27.2% with 95% CI (18.4%, 37.4%).
Overall correct selection (A+D)/(A+B+C+D): 1508/1772 = 85.1% with 95% CI (83.4%, 86.7%).
Applicant-defined correct selection (A+D)/(A+B+D): 1508/1575 = 95.7% with 95% CI (94.6%, 96.7%).
Correct selection among selectors: A/(A+B): 1483/1550 = 95.7% with 95% CI (94.5%, 96.6%).
Abbreviations: CI, confidence interval; N, number of subjects

5.13.4 Self-Selection for Limited Literacy Group

Table 24. Self-Selection in Actual Use Study: Limited Literacy Group, Applicant's Self-Selection Table

Self-Selection Population N=226	Appropriate or Acceptable to Use N=216	Not Appropriate to Use N=10
Selector/potential selector (N=174)	Cell A N=169	Cell B N=5
Non-selector (N=52)	Cell C N=47	Cell D N=5

Source: FDA reviewers' table
Correct deselection D/(B+D): 5/10 = 50.0% with 95% CI (18.7%, 81.3%).
Overall correct selection (A+D)/(A+B+C+D): 174/226 = 77.0% with 95% CI (70.9%, 82.3%).
Applicant-defined correct selection: (A+D)/(A+B+D): 174/179 = 97.2% with 95% CI (93.6%, 99.1%).
Abbreviations: CI, confidence interval; N, number of subjects

Table 25. Self-Selection in Actual Use Study: Limited Literacy Group, Reviewer's Self-Selection

Self-Selection Population N=226	Appropriate or Acceptable to Use N=213	Not Appropriate to Use N=13
Selector/potential selector (N=205)	Cell A N=195	Cell B N=10
Non-selector (N=21)	Cell C N=18	Cell D N=3

Source: FDA reviewers' table
Correct deselection D/(B+D): 3/13 = 23.1% with 95% CI (0.05%, 53.8%).
Overall correct selection (A+D)/(A+B+C+D): 198/226 = 87.6% with 95% CI (82.6%, 91.6%).
Applicant-defined correct selection: (A+D)/(A+B+D): 198/208 = 95.2% with 95% CI (91.3%, 97.7%).
Correct selection among selectors: A/(A+B): 195/205 = 95.1% with 95% CI (91.2%, 97.6%).
Abbreviations: CI, confidence interval; N, number of subjects

5.14 Use Phase of ACCESS Actual Use Study

5.14.1 Tables

Table 26. ACCESS Actual Use Study (AUS): Demographics of User Population

Demographic Characteristic	User Population (N=883)
Race[1]	
American Indian or Alaska Native	24 (2.7%)
Asian	50 (5.7%)
Black or African American	267 (30.2%)
Native Hawaiian or other Pacific Islander	12 (1.4%)
White	527 (59.7%)
Other	57 (6.5%)
Refused	8 (0.9%)
Age group/gender category	
Female age 11-14	49 (5.5%)
Female age 15-17	151 (17.1%)
Female age 18-19	76 (8.6%)
Female age 20-24	195 (22.1%)
Female age 25-34	259 (29.3%)
Female age 35+	153 (17.3%)
Female age 35-45	139 (15.7%)
Female age 46-55	12 (1.4%)
Female age 56+	2 (0.2%)
Age distribution	
Mean	25.5
SD	8.59
Median	24.0
Range	12, 61
Health literacy	
Normal[2]	763 (86.4%)
Low[3]	120 (13.6%)
History of HBC Use	
History of HBC use	633 (71.7%)
History of oral contraceptive use	543 (61.5%)
No history of oral contraceptive use	90 (10.2%)
No history of HBC use	250 (28.3%)
Education level (18+)	
Eighth grade or less	2 (0.2%)
Some high school	21 (2.4%)
High school graduate or GED	158 (17.9%)
Some college or technical school	315 (35.7%)
College graduate	156 (17.7%)
Post-graduate degree	31 (3.5%)
Estimated annual household income	

Demographic Characteristic	User Population (N=883)
Less than $25,000	282 (31.9%)
$25,001-$50,000	297 (33.6%)
$50,001-$75,000	124 (14.0%)
$75,001-$100,000	53 (6.0%)
$100,001-$150,000	51 (5.8%)
More than $150,000	19 (2.2%)
Don't know	56 (6.3%)
Refused	1 (0.1%)

Source: Adapted from Applicant's Table, Module 5.3.5.2, page 93, Table 14.2.1 ACCESS Clinical Study Report, NDA 017031 S-041 stamp date June 14, 2022.
[1] Answers below are not mutually exclusive
[2] Scored at least 61 on the REALM Test or REALM Teen Test.
[3] Scored at most 60 on the REALM Test or REALM Teen Test. These participants are referred to as having limited literacy in the text of this document.
User population: Participants who reported use of at least one dose of study medication in the e-diary during the study.
Abbreviations: GED, general educational development; HBC, hormonal birth control; N, number of participants; REALM, Rapid Estimate of Adult Literacy in Medicine; SD, standard deviation

Table 27. ACCESS AUS: Demographics of Adolescent User Population by Age

	Screening Population (N=1886)	Self-Selection Population (N=1772)	Purchaser Population (N=955)	Safety Population (N=955)	User Population (N=883)
Range	11, 68	12, 68	12, 61	12, 61	12, 61
Female Participants Age 11-19 by Age					
Age 11	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Age 12	5 (0.3%)	4 (0.2%)	4 (0.4%)	4 (0.4%)	3 (0.3%)
Age 13	42 (2.2%)	36 (2.0%)	16 (1.7%)	16 (1.7%)	16 (1.8%)
Age 14	53 (2.8%)	48 (2.7%)	31 (3.2%)	31 (3.2%)	30 (3.4%)
Age 15	54 (2.9%)	44 (2.5%)	24 (2.5%)	24 (2.5%)	22 (2.5%)
Age 16	87 (4.6%)	79 (4.5%)	46 (4.8%)	46 (4.8%)	43 (4.9%)
Age 17	163 (8.6%)	152 (8.6%)	94 (9.8%)	94 (9.8%)	86 (9.7%)
Age 18	75 (4.0%)	67 (3.8%)	41 (4.3%)	41 (4.3%)	38 (4.3%)
Age 19	69 (3.7%)	66 (3.7%)	38 (4.0%)	38 (4.0%)	38 (4.3%)

Source: Applicant's Table 14.2.1 in the ACCESS Clinical Study Report Module 5.3.5.2 sNDA 017031 S-041 stamp date June 14, 2022.
Abbreviations: ACCESS AUS, Adherence with Continuous-dose Oral Contraceptive: Evaluation of Self-Selection and Use actual use study; N, number of subjects

Table 28. ACCESS AUS: Disposition of Purchaser Population

	All Subjects (N=955)
Did not use the product	72 (7.5%)
Used the product at least once [6]	883 (92.5%)
Week 2 interim interview completed	850 (89.0%)
Week 4 interim interview completed	836 (87.5%)
Week 8 interim interview completed	739 (77.4%)
Week 12 interim interview completed	654 (68.5%)
Week 16 interim interview completed	583 (61.0%)
Week 20 interim interview completed	518 (54.2%)
Week 24 interim interview completed	471 (49.3%)
EOS telephone interview completed	642 (67.2%)
EOS onsite interview completed	70 (7.3%)
EOS home pregnancy test results known	410 (42.9%)

Source: Applicant's Table 14.1.3 in the ACCESS Clinical Study Report p. 26/1508, Module 5.3.5.2; NDA 017031 S-041 stamp date June 14, 2022.
[1] Completed subjects are defined as subjects who start the EOS telephone interview.
[2] Missing E-diary days are not considered as part of this disposition.
[3] Answers below are not mutually exclusive.
[4] Incomplete subjects are defined as all subjects who do not start the EOS telephone interview.
[5] Answers below are mutually exclusive.
[6] User population.
Abbreviations: AE, adverse event; EOS, end-of-study; N, number of subjects; PG, pregnancy; SAE, serious adverse event

Table 29. ACCESS AUS: Secondary Endpoints B, C, and D—Applicant's Analysis and FDA's Analysis

Secondary Endpoint	Analysis	Applicant's Result % Correct with 95% CI	FDA Analysis: Excludes Participants With Improbable Dosing % Correct with 95% CI	FDA's Sensitivity Analysis: Classifies Participants With Improbable Dosing as Incorrect % Correct with 95% CI
Endpoint B: (Proportion of AUSDs on which a tablet was taken or no tablet was taken and the participant reported a mitigating behavior[1] for following 2 calendar days)	Per-protocol	97.1 (97.0, 97.2)	96.8 (96.6, 96.9)	65.5 (65.2, 65.8)
	Worst-case	90.8 (90.6,90.9)	90.1 (89.9, 90.3)	61.2 (60.9, 61.5)
Endpoint C: (Proportion of participants who reported ≥85% adherence to taking study drug every day or reported a mitigating behavior when no tablet was taken)	Per-protocol	94.8 (93.1, 96.2)	94.5 (92.4,96.2)	66.6 (63.4, 69.7)
	Worst-case	79.5 (76.7, 82.1)	78.3 (74.8, 81.5)	55.2 (51.8, 58.5)

Secondary Endpoint	Analysis	Applicant's Result % Correct with 95% CI	FDA Analysis: Excludes Participants With Improbable Dosing % Correct with 95% CI	FDA's Sensitivity Analysis: Classifies Participants With Improbable Dosing as Incorrect % Correct with 95% CI
Secondary Endpoint D: (Proportion of participants who reported use of study drug within 27 h of the previous dose or reported a mitigating behavior when a tablet was not taken within 27 h of previous dose)	Per-protocol	99.0 (98.9, 99.1)	98.9 (98.8, 99.0)	66.1 (65.8, 66.5)
	Worst-case	89.3 (89.1,89.5)	88.5 (88.2, 88.7)	59.7 (59.4, 60.0)

Source: FDA review team using data from the Access Clinical Study Report Module 5.3.5.2 NDA 017031 S-041, stamp date June 14, 2022 and ACCESS Root Cause Analysis of Improbable Dosing, NDA 017031 eCTD sequence 0094, stamp date October 13, 2022.

[1] Mitigating behavior: using a condom (or another barrier method) for any act of intercourse or abstaining from intercourse for the following 2 calendar days.

Note: worst-case analysis: classifies all days with missing data as incorrect.

Abbreviations: ACCESS AUS, Adherence with Continuous-dose Oral Contraceptive: Evaluation of Self-Selection and Use actual use study; AUSD, active use study day (all study days between and including a participant's first and last use of study drug as reported in the e-diary); CI, confidence interval; h, hour

Table 30. ACCESS AUS: Secondary Endpoints E to P—Applicant's Analyses, FDA-Requested Analyses, and FDA-Conducted Analyses

Secondary Endpoint	Applicant's Analysis as Presented in ACCESS Clinical Study Report in sNDA Submission	FDA's Analysis or FDA-Requested Analysis Submitted by Applicant	Differences in Applicant and FDA Analyses
Secondary Endpoint E (proportion of pack transitions where the participant did not report a break between packs)	92.3% (2,057/2,229) 95% CI (91.1,93.4)	FDA's worst-case sensitivity analysis: 85.8% (2,057/2,397)	**FDA's sensitivity analysis:** Includes all pack transitions in the denominator. **Applicant's analysis**: Includes only transitions where participant reported on their use of the study drug on the day after completing a pack in the denominator.
Secondary Endpoint F (proportion of participants who did not use study drug together with another hormonal contraceptive)	98.8% (872/883) 95% CI (97.8, 99.4)	Not applicable	No difference in analysis by FDA and Applicant

Secondary Endpoint	Applicant's Analysis as Presented in ACCESS Clinical Study Report in sNDA Submission	FDA's Analysis or FDA-Requested Analysis Submitted by Applicant	Differences in Applicant and FDA Analyses
Secondary Endpoint G (proportion of participants who used a barrier method of contraception or abstained from intercourse for the first 48 h when initiating therapy)	79.7% (543/681) 95% CI (76.5,82.7)	FDA worst-case sensitivity analysis: 61.5% (543/883)	**FDA's sensitivity analysis:** Includes all participants in the User Population in the denominator. **Applicant's analysis**: Only includes participants who reported on their sexual activity on the day they started the drug and the day after in the denominator.
Secondary Endpoint H (proportion of participants who were taking one of the drugs listed in the "ask a doctor or pharmacist before use" (AADPBU) section of the label and completed the correct action)	55% (11/20) (Correct)[3] 95.0% (19/20) (Correct and acceptable)[4] 95% CI (75.1,99.9)	FDA's Analysis: 10% (2/20)	**FDA's analysis:** Classifies participants who did not select the drug and cited the AADPBU warning as reason for deselection as correct. **Applicant's analysis**: classifies participants who did not select and cited the AADPBU warning as the reason for deselection or who reported contacting a HCP (for any reason and not just about use of the AADPBU product) during the study as correct. The timing of when the discussion with the healthcare provider occurred in relation to starting the study drug is unknown.
Secondary Endpoint I (proportion of participants who became pregnant before use or during use of the study drug who stopped use within three days of finding out about the pregnancy and reported talking with a healthcare provider during the study)	Correct: 100% (6/6) 95% CI (54.1, 100.0)	Correct: 80% (8/10)	**FDA analysis:** Includes the ten participants determined by the FDA review team to have become pregnant pre-treatment or on-treatment. **Applicant's analysis:** Includes the six participants the Applicant classified as becoming pregnant pre-treatment or on-treatment.
Secondary Endpoint J (proportion of participants who reported sudden or severe pain in the lower abdomen during the study who reported seeking healthcare)	66.7% (6/9) 95% CI (29.9,92.5)	33.3% (3/9)	**FDA-Requested analysis:** only classifies participants who spoke to a HCP about abdominal pain as correct rather than participants who spoke to a HCP for any reason at any time during the study. **Applicant's analysis:** Classifies all participants who spoke to a HCP for any reason at any time during the study as correct.

Secondary Endpoint	Applicant's Analysis as Presented in ACCESS Clinical Study Report in sNDA Submission	FDA's Analysis or FDA-Requested Analysis Submitted by Applicant	Differences in Applicant and FDA Analyses
Secondary Endpoint K (proportion of participants who reported a late period after missing any tablets in the last month or reported not having a period for 2 months and who performed a correct action)	70.7% (41/58) 95% CI (57.3,81.9)	70.7% (41/58)	**FDA-Requested analysis**: classifies participants who spoke to a healthcare provider about late or missed periods or took a pregnancy test as correct. **Applicant's analysis:** classifies participants who either stopped use of the study drug or spoke to a healthcare provider about late or missed periods or took a pregnancy test as correct. (Numerator and denominator unchanged in FDA-requested analysis due to overlap of actions classified as correct).
Secondary Endpoint L (proportion of participants who reported unusually heavy periods or periods that last more than 8 days who reported taking the correct action)	71.1% (32/45) 95% CI (55.7,83.6)	FDA requested analysis: 18% (9/50)	**FDA-requested analysis**: classifies participants who consulted a HCP about their heavy periods or periods that last >8 days as correct and does not include participants who stopped the study drug in the numerator. The FDA analysis also includes all participants who reported heavy or prolonged periods during the study. **Applicant's analysis:** classifies all participants who stopped study drug or consulted a HCP for any reason at any time during the study as correct. The Applicant's analysis only includes participants who completed the EOS interview and reported heavy or prolonged periods during the study.
Secondary Endpoint M (proportion of participants who reported repeated vaginal bleeding brought on by sexual intercourse who spoke to a HCP)	50% (1/2)	0% (0/2)	**FDA-requested analysis** only classifies participants who spoke to a HCP about vaginal bleeding brought on by sexual intercourse as correct. **Applicant's analysis:** classifies participants who spoke to a HCP for any reason at any time during the study as correct.

Secondary Endpoint	Applicant's Analysis as Presented in ACCESS Clinical Study Report in sNDA Submission	FDA's Analysis or FDA-Requested Analysis Submitted by Applicant	Differences in Applicant and FDA Analyses
Secondary Endpoint N (proportion of participants who reported new migraines with aura or whose migraines got worse who spoke to a HCP)	77.8% (7/9)	FDA-requested analysis A: 45.5% (5/11)	**FDA-requested analysis A**: only classifies participants who spoke to a HCP about their migraines as correct. FDA analysis includes all participants who reported new or worsening migraines during the study in the analysis. **Applicant's analysis:** classifies participants who spoke to a HCP for any reason at any time during the study as correct. Applicant's analysis only includes participants who completed the EOS interview.
Secondary Endpoint O (proportion of participants who developed yellowing of the skin or whites of the eyes who reported seeking healthcare and stopped use)	Unable to be assessed as there were no participants experiencing these symptoms	Not applicable	
Secondary Endpoint P (proportion of pregnancies in the User Population that occurred while taking the product)	54.5% (6/11)	81.8% (9/11)	**FDA analysis**: Three additional pregnancies were classified as occurring while on-treatment by the FDA review team and are included in the numerator of the FDA analysis.

Source: FDA review team from data from the ACCESS Clinical Study Report, Module 5.3.5.2, NDA 017031 S-041, stamp date June 14, 2022 and Applicant's response to IR #44 dated January 10, 2023, NDA 017031 eCTD sequence number 107 ACCESS: adherence with continuous-dose oral contraceptive: evaluation of self-selection and Use; HCP: healthcare provider; AADPBU: ask a doctor or pharmacist before use.
Abbreviations: AADPBU, ask a doctor or pharmacist before use; ACCESS AUS, Adherence with Continuous-dose Oral Contraceptive: Evaluation of Self-Selection and Use actual use study; EOS, end-of-study; HCP, health care provider

5.14.2 Discussion of Secondary Endpoints F, G, J, and L

Secondary Endpoint F (Do Not Use With Other Hormonal Birth Control Products)

The corresponding message on the tested DFL instructs consumers to not use the product "together with another birth control pill, vaginal ring, patch, implant, injection or an IUD (intra-uterine device)."

Endpoint Definition: The denominator is the User Population, and the numerator is all women who appropriately did not use the study drug together with another form of hormone-containing birth control or a hormone-containing IUD at any time during the active use period.

The Applicant reported that 98.8% (872/883) participants belonging to the User Population reported not using another hormone-containing birth control product while using the study drug (lower bound of the 95% CI of 97.8%). Eight of the 11 participants who reported using a hormone-containing birth control product while using the study drug reported using a hormone-containing birth control product at

enrollment while three of the 11 participants initiated use of another hormone-containing birth control product or IUD after enrolling in the study. Eight of the 11 participants (including those that initiated use of another hormone-containing birth control product during the study) did not report stopping use of the other hormonal birth control product during the study. The types of hormone-containing birth control reported to be used concomitantly with the study drug included Depo Provera (medroxyprogesterone acetate 150 mg), Nexplanon (etonorgestrel 68 mg implant), Mirena (levonorgestrel 52 mg) IUD, Plan B (levonorgestrel 1.5 mg), Kyleena (levonorgestrel 19.5 mg) IUD, and Junel Fe (norethindrone 1 mg and ethinyl estradiol 20 μg).

Secondary Endpoint G (Using a Barrier Method of Contraception for the First 48 Hours When Initiating Therapy)

The corresponding message on the tested DFL instructs consumers to "use a condom (or another barrier method) every time you have sex during the first 2 days of use (48 hours) after you start your first pack of this product, because it takes 2 days for this product to start working."

Endpoint Definition: The denominator is all users of the study drug, and the numerator is all participants who either reported using a condom (or another barrier method of birth control) if they had intercourse or who abstained from intercourse for the first 48 hours after starting the study drug.

The Applicant reported that a total of 79.7% (543/681) of evaluable participants (95% CI lower bound 76.5%, upper bound 82.7%) in the User Population followed the label instruction to use a barrier method of contraception for the first 48 hours after starting the product. This analysis included 490 participants who reported not having sex in the first 48 hours after starting the study drug and 53 participants who reported using a condom or barrier method each time they had sex during the first 48 hours after starting the study drug. The Applicant noted that there were a total of 202 participants belonging to the User Population who were excluded from this analysis because they did not report on their sexual activity on the day they started the drug and the day after. Of these participants, 188 were participants under the age of 18, who were not supposed to be asked about sexual activity per-protocol, and 14 participants were adults who did not report on their sexual activity on the Active Use Period Start Date and the following day. The FDA review team conducted a worst-case sensitivity analysis of Secondary Endpoint G using all participants belonging to the User Population in the denominator as this is the most conservative estimate for this endpoint where all participants who did not report on sexual activity on the start day and day after were classified as incorrect. The FDA conducted worst-case analysis resulted in 61.5% (543/883) of all participants in the User Population who reported using a condom (or another barrier method of birth control) if they had intercourse or who abstained from intercourse for the first 48 hours after starting the study drug.

Table 31. Applicant's Analysis and FDA's Worst-Case Sensitivity Analysis of Secondary Endpoint G (Using a Barrier Method of Contraception or Abstaining from Intercourse When Initiating Therapy)

Applicant's Analysis	FDA Worst-Case Sensitivity Analysis
79.7% (543/681)	61.5% (543/883)[1]

Source: FDA review team from data from the ACCESS Clinical Study Report Module 5.3.5.2; sNDA 017031 stamp date June 14, 2022.
[1] FDA's worst-case analysis classifies all participants who did not report on sexual activity on day of and day after initiation of study drug as incorrect.
Abbreviations: ACCESS, Adherence with Continuous-dose Oral Contraceptive: Evaluation of Self-Selection and Use; FDA, Food and Drug Administration

Notably, of the 191 participants who reported having sex during the first 48 hours after starting norgestrel, 72.3% (138/191) reported not using a condom or barrier method each time they had sex during the first 48 hours after starting the study drug.

Secondary Endpoint J (Talk to a Doctor if You Have Sudden or Severe Pain in Your Lower Belly)

The corresponding message on the tested DFL instructs consumers to talk to a doctor if you "have sudden or severe pain in your lower belly—see a doctor immediately (you could have an ectopic pregnancy).

Endpoint definition: The denominator for Secondary Endpoint J includes all users who reported experiencing sudden or severe pain in their lower belly during the study and completed the study (i.e., answered the relevant EOS telephone interview questions) and the numerator is all such participants who reported seeking healthcare. Note that participants who spoke to a HCP for any reason (rather than only participants who spoke to a HCP about their abdominal pain) were classified as performing a correct behavior.

Of the nine participants who reported sudden or severe pain in their lower belly at the EOS interview or through spontaneous reporting of an AE during the nurse interim interviews, the Applicant reported 66.7% (6/9) as the result of the Secondary Endpoint J endpoint analysis as this was the proportion of participants who reported speaking to a HCP during the study. Notably, all participants who performed the action of speaking to a HCP, regardless of whether they spoke to a HCP about their abdominal pain, were considered to have performed a correct action and included in the numerator. The FDA review team requested the Applicant for an analysis of this endpoint using the FDA review team's definition. The FDA-requested analysis result was that 33.3% (3/9) of participants who endorsed sudden or severe pain in the lower abdomen spoke to a HCP about their symptoms. Of these three participants, only one participant spoke to a HCP on the same day.

Table 32. Applicant and FDA-Requested Analysis of Secondary Endpoint J (Sudden or Severe Abdominal Pain)

Applicant's Analysis	FDA-Requested Analysis
66.7% (6/9)[1]	33.3% (3/9)[2]

Source: FDA review team from data in the Applicant's response to IR#44 dated January 10, 2023 NDA 017031 eCTD sequence number 107.
[1] Applicant's Analysis classifies participants who spoke to a HCP for any reason at any point during the study as correct.
[2] FDA-requested analysis only classifies participants who spoke to a HCP about abdominal pain as correct.
Abbreviations: eCTD, electronic common technical document; FDA, Food and Drug Administration; HCP, health care provider; IR, information request

Secondary Endpoint L (Talk to a Doctor and Continue Taking Every Day if You Have Unusually Heavy Periods or Periods That Last More Than 8 Days)

The corresponding message on the tested DFL instructs consumers to talk to a doctor and continue taking every day if they experience periods that last more than eight days or are unusually heavy.

Endpoint definition: The numerator consisted of participants who had unusually heavy periods or periods lasting more than eight days AND completed the study AND either spoke to a HCP or stopped using the study drug. The denominator was comprised of participants who reported having unusually heavy periods or periods lasting more than eight days and completed the study (i.e., answered the relevant EOS telephone interview questions).

In the ACCESS Clinical Study Report, the Applicant presented this endpoint analysis as 71.5% (32/45) of participants in the User Population who reported unusually heavy periods or periods lasting more than eight days and who completed the study, spoke with a HCP or stopped use of the study drug (lower bound of the 95% CI of 55.7%). Notably, all participants who spoke to a HCP for any reason at any time during the study were categorized as correct and included in the numerator. Notably two participants who were assessed by the Applicant as correct in this endpoint analysis had an interaction with a HCP that occurred before the report of prolonged or heavy periods.

The DFL warning instructs consumers to talk to a doctor AND continue taking every day if they have periods that last more than eight days or are unusually heavy so that participants can receive the medical evaluation they need and not compromise the efficacy obtained from this product. The Applicant categorized participants who stopped using the product as correct. The most important safety issue for concern in participants who have unusually heavy periods is an undiagnosed medical condition such as malignancy that warrants medical evaluation. Whether stopping the drug and observing for cessation of symptoms may be acceptable is dependent on many factors including age, risk factors, past medical history, comorbidities, family history, and clinical course. Notably, in the prescription setting, patients already have a HCP who is familiar with their medical history and prescribed this drug. In the nonprescription setting, it is likely that many consumers may have barriers to accessing a HCP and any delay that stems from misattribution of bleeding changes to the study drug may potentially increase the consumers risk for worse clinical outcomes. The FDA review team requested that the Applicant conduct an analysis which classified only participants who spoke to a HCP specifically about their heavy periods or periods lasting more than eight days as correct in the numerator and to include all 50 participants who reported having unusually heavy periods or periods lasting more than 8 days in the denominator rather than participants that only completed the EOS interview. This yielded a result of 18.0% (9/50; 95% CI 8.6% to 31.4%).

Table 33. Applicant and FDA-Requested Analysis of Secondary Endpoint L (Unusually Heavy Periods)

Applicant's Analysis[1]	FDA-Requested Analysis[2] (Numerator and Denominator Redefined)
71.5% (31/45)	18.0% (9/50)

Source: FDA review team from data in the Applicant's response to IR#44 dated January 10, 2023 NDA 017031 eCTD sequence number 107.

[1] Applicant's analysis: numerator consisted of participants who had unusually heavy periods or periods lasting more than eight days AND completed the EOS interview AND either spoke to a healthcare provider (for any reason) or stopped using the study drug. The denominator was comprised of participants who reported having unusually heavy periods or periods lasting more than eight days and completed the EOS interview.

[2] FDA-requested analysis: numerator: all participants who consulted a healthcare provider about unusually heavy periods or periods lasting more than eight days; denominator: includes all participants who only reported unusually heavy periods or periods lasting more than 8 days during their participation in the study.

Abbreviations: eCTD, electronic common technical form; EOS, end-of-study; FDA, Food and Drug Administration; IR, information request

The Applicant also conducted an analysis where participants who consulted a HCP specifically about their symptoms and participants who discontinued use were classified as correct. This resulted in 50% (25/50) of all participants who reported heavy or prolonged periods during the course of the study as having stopped the study drug or spoken to a HCP about their symptoms. However, without further information on medical history, comorbidities, and access to follow-up data, it is unclear if stopping the study drug and observing for cessation of symptoms may have been an acceptable action for each individual participant.