U.S. FOOD & DRUG ADMINISTRATION

Joint Meeting of the Nonprescription Drugs Advisory Committee and the Obstetrics, Reproductive, and Urologic Drugs Advisory Committee

NDA 017031 S-041 / Opill (norgestrel) tablet, 0.075 mg

Day 1
May 9, 2023

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Introduction

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May 9, 2023

Supplemental NDA 017031-041

- **Supplemental new drug application for a first-in-class (daily oral contraceptive) prescription-to-nonprescription switch**
- **Norgestrel tablet 0.075 mg**
  - Progestin-only oral contraceptive pill (POP or POC)
  - Approved (prescription) since 1973 for the prevention of pregnancy in females of reproductive potential
  - Not marketed since 2005 for business reasons

Public Health Impact and Need

- Unintended pregnancies are common and have major public health effects
- An effective and accessible method for prevention of pregnancy is important for many U.S. females of reproductive potential
- Prescription daily oral contraceptives are widely used and effective
- Methods currently available without interaction with a healthcare provider may have more limited effectiveness

AC Meeting Objective

FDA is seeking advisory committee input on:

- Likelihood of safe and effective use of norgestrel tablet in nonprescription setting
- Appropriate consumer self-deselection

Products Amenable to Nonprescription Use

- Labeling alone is adequate to enable consumers to
  - Self-select
  - Use properly and take as directed by the drug facts label
  - Know when to stop use or contact a healthcare provider
- Low potential for misuse and abuse

Switch Application Approval Standards

- **Effectiveness of the drug must outweigh the risks in a nonprescription setting where there is no**
  - Learned intermediary
  - Option to approve with a risk evaluation and mitigation strategy (REMS)
  - Behind-the-counter option
  - Option to approve with requirements for additional studies after approval (postmarketing requirements)
    - Changes to labeling based on additional testing

Issues to Consider in AC Meeting

- Correct use of the product is required to prevent pregnancy and data are needed to inform likely effectiveness
  - Incorrect use (even with infrequent missed tablets) can result in unintended pregnancy
    - Additional considerations for adolescents and limited literacy subpopulations
- Risks of inappropriate use in consumers with
  - Progestin-sensitive cancer
  - Vaginal bleeding of undiagnosed etiology

We seek input from the Advisory Committee to help inform our regulatory decision on this supplemental application.

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Efficacy and Safety of Prescription Norgestrel Tablet and Implications for the Nonprescription Setting

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Contraceptive Methods*

- Emergency Contraception (EC)
- Intrauterine systems/devices (IUS/IUD), implants, injectables
- Tablets (pills), transdermal systems (patches), vaginal rings
  - Two hormones (progestin plus estrogen) (combined oral contraceptives or COCs)
  - One hormone (progestin only) (progestin-only contraceptives or POCs)
    - **Norgestrel tablet (POP)**
- On-demand and barrier methods (condoms, diaphragms/sponges, spermicides/vaginal gels)

*Not an exhaustive list

Outline

- Basis for original approval of prescription norgestrel tablet
- Dosing and administration considerations
- Estimating effectiveness for the nonprescription setting
- Key safety concerns for the nonprescription setting
- Translating effective and safe use to the nonprescription setting

Original Approval of Norgestrel for the Prescription Setting

- Efficacy and safety established with original approval (1973)
- Post-approval data available until 2005
- Eight clinical studies conducted in the U.S. supported approval
  - Efficacy: Pearl Index (pregnancy calculation) was 2.3 per 100 woman-years
  - Safety: Exposure in 2,173 participants over 21,856 treatment cycles
  - Dosing regimen evaluated: one tablet taken at the same time every day

Approved for females of reproductive potential of **all** ages

Norgestrel Tablet: Approved Dosing and Administration Instructions (Opill USPI* 2017)

- Take one tablet daily at the same time each day
- Take a delayed or missed tablet as soon as possible and continue with the next dose
- Take norgestrel tablet continuously (no break between packs)
- Use of additional nonhormonal contraception is needed for the **next 48 hours** when:
  1. Taken 3 or more hours late or missed
  2. Vomiting or diarrhea occurs within 4 hours after taking the tablet

*USPI: United States Prescribing Information

OVERVIEW OF EFFECTIVENESS AND IMPLICATIONS FOR THE NONPRESCRIPTION SETTING

Effectiveness: Overview

- Overview of primary efficacy endpoint (Pearl Index) from the prescription setting
- Estimating effectiveness of norgestrel tablet in the nonprescription setting
  - Factors affecting effectiveness of norgestrel tablet
  - Available sources of data
- Remaining questions for the nonprescription setting

Pearl Index (PI)

- Contraceptive efficacy endpoint of interest
- Used to demonstrate effectiveness to support approval since approval of the first oral contraceptive product
- Usually reported as the number of pregnancies out of a total of 100 women

Pearl Index Calculation

$$\text{Pearl Index} = \frac{(\text{Number of pregnancies}) \times 13}{\text{cycles}} \times 100$$

$$\text{Number of 28-day cycles}$$

To demonstrate effectiveness for a new contraceptive product, PI calculation considers:

- Numerator (Number of pregnancies): Defined as any pregnancy occurring while taking the product (“on-treatment pregnancy”)
- Denominator (Number of cycles): Cycles where intercourse occurred, and no backup contraceptive was used (“evaluable cycles”)

Pearl Index: Statistical Considerations

Methodologies differ between the analysis used in the original approval (1973) and current FDA clinical trial recommendations for approval of contraceptives

Original Approval (1973)	Present Day
Includes ALL females ages 15-49 years	Includes ONLY females up to age 35 years†
Includes ALL menstrual cycles	Includes ONLY evaluable cycles‡

† Cutoff of age 35 years and greater based on decreased likelihood that a female will become pregnant.
‡ Evaluable cycles are defined as cycles where at least one episode of vaginal intercourse occurred and additional nonhormonal (e.g., barrier contraception such as condoms) or emergency contraception was not used.

Factors Affecting Effectiveness of Norgestrel Tablet

Extrinsic Factors (modifiable)

- Adherence:
  - Contraceptive efficacy of norgestrel highly dependent on strict adherence to dosing regimen

Intrinsic Factors (non-modifiable)

- Population characteristics:
  - Body mass index (BMI)
  - Prevalence may change over time

Effectiveness: Importance of Adherence to Dosing Instructions

- Need for adherence to daily dosing regimen based on:
  - Short elimination half-life → serum progestin levels near baseline 24 hours after oral intake
  - Low steady-state progestin levels
  - Large variations in serum levels among individual users

Importance of Adherence to Dosing Regimen: Comparing POPs and COCs

	POPs (such as norgestrel tablet)	Combined Oral Contraceptives
Primary mechanism(s)	Ovulation suppression Cervical mucus effects	Ovulation suppression
Ovulation suppression	40-60%	>90%
Suppression of mid-cycle luteinizing hormone (LH) and follicle-stimulating hormone (FSH) peak	Lower	Higher
Steady-state serum progestin levels	Lower	Higher

POPs such as norgestrel demonstrate lower ovulation suppression than COCs. POP mechanism may include cervical mucus effects; must maintain continuous exposure to progestin for optimal contraceptive efficacy.

Delayed Pill Intake Study: Phase 2 - Pharmacodynamic Study

- Study 151042-002 (or Study 002): impact of delayed intake and missed pill on cervical mucus and ovarian activity
- Limitations:
  - Cervical mucus and ovarian activity scores are not primary measures of contraceptive efficacy
  - Lacks generalizability (small sample size; excluded females with BMI > 32 kg/m^2)
- Conclusion: Study 002 design cannot demonstrate that delayed intake does not alter the risk of pregnancy

Effectiveness: Impact of a Changing Population

- Prevalence of obesity has increased dramatically since norgestrel was approved as a contraceptive:
  - 13% in 1960 vs. 42% in 2021
- Increasing BMI associated with decreasing efficacy of hormonal contraceptives (Yamazaki et al. 2015)

Yamazaki M, Dwyer K, Sobhan M, Davis D, Kim MJ, Soule L, Willett G, Yu C. Effect of obesity on the effectiveness of hormonal contraceptives: an individual participant data meta-analysis. Contraception. 2015 Nov;92(5):445-52.

Estimating Effectiveness of Norgestrel Tablet in the Nonprescription Setting: Available Sources of Data

- Eight clinical trials (original approval 1973)
- Published literature (including Applicant's meta-analysis)
  - A limited number of clinical studies attempt to describe efficacy of norgestrel in the post-approval prescription setting
- ACCESS Actual Use Study (AUS)
  - A multi-center, open-label study conducted by the Applicant to assess consumer use behaviors in real-world setting

Pearl Index (PI): Results for Norgestrel Tablet

Source of Data	Pearl Index (per 100 Women-Years)
Prescription Setting	
Original Approval (1973)	2.3 (1.5, 3.0)
Meta-analysis (through 2020)	1.96 (Range: 1.18 to 6.87)
Nonprescription Setting	
ACCESS Actual Use Study (AUS) – **Applicant** Analysis	2.2 (0.8, 4.8)
ACCESS Actual Use Study – **FDA** Analysis	3.4 (1.6, 6.4)

Effectiveness of Norgestrel Tablet in Published Literature

- Applicant conducted a meta-analysis to inform effectiveness of norgestrel tablet in the current U.S. population
- Limitations include:
  - Heterogeneity of study designs
  - Lack of generalizability to current U.S. population
  - Inconsistent methodologies across studies
  - Varying study durations (range 6 months to 5 years)
  - Inclusion of lactating females in some studies

Pearl Index: ACCESS AUS – FDA Analysis

- Numerator: 9 pregnancies (vs. 6 identified by Applicant)
  - 2 pregnancies in BMI 25 kg/m^2 to 29.9 kg/m^2
  - 3 pregnancies in BMI ≥ 30.0 kg/m^2
- Denominator:
  - Fewer cycles compared to Applicant analysis

ACCESS AUS Pearl Index Cannot Estimate Effectiveness of Norgestrel Tablet in the Nonprescription Setting

Limitations:

- Small sample size → lacks precision
- High discontinuation rates (50%)
- Includes ALL menstrual cycles (not evaluable cycles)
- Sexual history and sexual activity not recorded for adolescents → risk for pregnancy unknown
- Improbable dosing

Summary: Effectiveness

The expected contraceptive efficacy of norgestrel tablet as a nonprescription product for prevention of pregnancy is unknown because:

- Available data from the prescription setting may not adequately inform effectiveness in the nonprescription setting in today's population
- Adherence to dosing instructions is determined by consumer behavior
- Increasing BMI in U.S. population may result in a higher PI than originally identified in clinical trials for approval
- Limitations of data from ACCESS AUS preclude extrapolation of the PI

REVIEW OF SAFETY AND IMPLICATIONS FOR THE NONPRESCRIPTION SETTING

Safety: Overview

- Known safety profile of norgestrel tablet
- Primary safety considerations for the nonprescription setting
- Additional considerations for the nonprescription setting

Norgestrel Tablet (Opill) Prescribing Information*: Contraindications

- Breast cancer, or other progestin-sensitive cancer, now or in the past
- Known or suspected pregnancy
- Abnormal vaginal bleeding of undiagnosed etiology
- Hypersensitivity (FD&C Yellow No.5 [tartrazine])
- Benign or malignant liver tumors

*Updated 2017

Norgestrel Tablet (Opill) Prescribing Information: Warnings/Precautions

- Ectopic pregnancy
- Delayed follicular atresia/ovarian cysts
- Bleeding pattern alterations
- Hepatic neoplasia/liver disease
- Migraine/headache
- Drug interactions
- Gastrointestinal disturbance
- Interactions with laboratory tests
- Carbohydrate and lipid effects

Nonprescription Setting Considerations

Important Safety Concerns

- Breast cancer, or other progestin-sensitive cancer
- Abnormal vaginal bleeding of undiagnosed etiology
- Bleeding pattern alterations
- Drug interactions

Additional Considerations

- Use in adolescents (approved for use as a prescription product)
- Potential impact on bone mineral density (BMD)
- Current use of hormonal contraceptives or (IUS)/(IUDs)

Progestin Use and Potential Risk of Breast Cancer (and Other Progestin-Sensitive Cancers)

- Norgestrel use may increase the risk of recurrence or stimulate the growth of an undiagnosed progestin-sensitive tumor
  - Nonclinical (animal) data demonstrate stimulated growth and metastasis of breast cancer with exposure to progestins (Patel and Schwarz 2012)
- Insufficient clinical data to estimate change in relative risk of these cancers with chronic norgestrel use

Patel A, Schwarz EB; Society of Family Planning. Cancer and contraception. Release date May 2012. SFP Guideline #20121. Contraception. 2012 Sep;86(3):191-8.

Potential Impact of Norgestrel Use in Females Under Age 50 with Progestin-Sensitive Cancers

Cancer Type	Prevalence	Incidence	Population Trend
Breast	0.2% (N=260,316)	48.6 per 100,000	↑
Melanoma	0.1% (N=106,680)	8.1 per 100,000	Not significant
Meningioma (non-malignant)	n/a	4.3 per 100,000	↑
Adenocarcinoma of the lung	< 0.1% (N=3,536)	1.3 per 100,000	↓

Surveillance, Epidemiology, and End Results Program. 2019. National Cancer Institute, National Institutes of Health. SEER*Explorer Application (cancer.gov). Accessed August 18, 2022 and April 14, 2023.

Abnormal Vaginal Bleeding of Undiagnosed Etiology: Definition

- Defined by relation to an individual's menstrual cycle
  - Timing: occurs on days that are outside an individual's normal menses (regularity and frequency)
  - Quantity: is heavier than an individual's normal menses
  - Duration: lasts longer than 8 days during an individual's normal menses

Abnormal Vaginal Bleeding of Undiagnosed Etiology: Causes

- Many conditions can cause abnormal vaginal bleeding including:
  1) Structural causes: polyps, adenomyosis, leiomyoma, endometrial hyperplasia, or malignancy
  2) Nonstructural causes: coagulopathy, ovulatory dysfunction, disorders of the endometrium, iatrogenic, or otherwise unidentified causes
  3) Pregnancy (intrauterine or ectopic)

Abnormal Vaginal Bleeding of Undiagnosed Etiology: Clinical Considerations

- Affects up to one-third of reproductive-age females in lifetime (Davis and Sparzak 2022)
- 30% of gynecology office visits annually (ACOG 2012)
- Endometrial cancer rare in reproductive age females
  - (0.037% in females under age 50) (SEER 2019)
- Norgestrel use may delay diagnosis and treatment

Davis E and PB Sparzak. Abnormal Uterine Bleeding. [Updated 2022 Sep 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532913/. Accessed April 17, 2023.
Committee on Practice Bulletins—Gynecology. Practice bulletin no. 128: Diagnosis of Abnormal Uterine bleeding in Reproductive-aged Women. Obstet Gynecol. 2012 Jul;120(1):197-206.
Surveillance, Epidemiology, and End Results Program. 2019. National Cancer Institute, National Institutes of Health. SEER*Explorer Application (cancer.gov). Accessed August 18, 2022.

Bleeding Pattern Alterations with Progestin Use (Such as Norgestrel Tablet): Etiology

- Absence of estrogen causes thinning of the endometrium
- Disruption of endometrial angiogenesis
- May result in irregular and unpredictable bleeding and sometimes absence of menstrual bleeding (amenorrhea)
- Frequent irregular menses and amenorrhea are often causes for discontinuation of POCs

Bleeding Pattern Alterations: Clinical Considerations

- Norgestrel use may cause changes in bleeding patterns that potentially result in:
  - Delayed diagnosis of pregnancy (ectopic or intrauterine) which may require urgent medical attention
  - Missed opportunities for timely use of emergency contraception
  - Delayed diagnosis of causes of abnormal vaginal bleeding that benefit from healthcare provider (HCP) evaluation
    - Structural (polyps, fibroids, etc.)
    - Nonstructural (thyroid disorders, polycystic ovarian syndrome)

Summary: Abnormal Vaginal Bleeding of Undiagnosed Etiology and Bleeding Pattern Alterations

- Abnormal vaginal bleeding and bleeding pattern alterations with norgestrel use may indicate condition(s) that require urgent medical attention such as ectopic pregnancy or miscarriage
- Nonprescription use may increase delayed evaluation by a HCP

Abnormal Vaginal Bleeding of Undiagnosed Etiology and Bleeding Pattern Alterations: Key Questions

- Will individuals choosing norgestrel be able to self-identify abnormal vaginal bleeding requiring HCP evaluation **prior** to initiation?
- Will individuals using norgestrel with bleeding pattern alterations be able to self-identify whether bleeding is abnormal requiring HCP evaluation?
- Will individuals understand norgestrel bleeding profile not the same as most COCs and seek timely care when abnormalities occur?

Drug Interactions With Norgestrel

- Many drugs and herbal products induce hepatic enzymes (e.g., CYP3A4)
  - Increases the metabolism of CYP3A4 substrates (including progestins such as norgestrel)
  - May decrease the contraceptive efficacy of norgestrel
- Norgestrel may also decrease the efficacy of other drugs, such as ulipristal acetate (emergency contraception)

Examples of Interacting Drugs

Drugs Known to Decrease Efficacy of Norgestrel	Conditions Drug Used to Treat
Phenytoin	Seizure disorder
Carbamazepine	Seizure disorder
Barbiturates	Anxiety, muscle spasms, seizure disorder
Rifampin	Tuberculosis
Efavirenz	HIV
Bosentan	Pulmonary hypertension
St. Johns Wort (herbal supplement)	Depression

Drug Interactions: Mitigating Measures

- If concomitant use with norgestrel cannot be avoided, current label recommends additional nonhormonal contraception (e.g., barrier such as condoms):
  1) When initiating and throughout concomitant use
  2) 28 days after discontinuation of the interacting drug
- If use of interacting drug is expected to be chronic, consider alternative method of contraception

Drug Interaction Mitigating Measures: Ulipristal Acetate

- Initiation of norgestrel within 5 days of ulipristal acetate (UA) for emergency contraception may decrease the effectiveness of UA
- Initiate norgestrel no sooner than 5 days after UA
- Use additional nonhormonal contraception until the next menstrual period

Use in adolescents, bone mineral density, current use of contraception

ADDITIONAL CONSIDERATIONS IN THE NONPRESCRIPTION SETTING

Use in Adolescents

Use in this population is of special interest because:

- Comprehension of key messages may differ by age group
- Sexual practices may differ compared to adults
- Missed opportunities for healthcare provider interactions and counseling

Prescription norgestrel tablet approved for use in females of reproductive potential of **all** ages.

Potential Impact of Progestins* on Bone Mineral Density (BMD)

Chronic unopposed progestin use → Hypoestrogenic state → decreased BMD (in users of any age)

- May reduce peak bone mass accretion in adolescents
- Magnitude of effect likely dependent on progestin structure, dose, and route of administration
- Recovery of BMD after discontinuation may depend on duration of exposure and potency of the specific progestin
- Potential impact of chronic use on fracture risk is unknown, particularly in adolescents

*Examples of commercially available progestins in the U.S. include: depot medroxyprogesterone acetate, norgestrel, norethindrone, levonorgestrel, desogestrel, etonogestrel, norgestimate, and drospirenone.

Current Use of Hormonal Contraception or Intrauterine System (IUS)

- To avoid unintended pregnancy:
  - Initiate norgestrel tablet use the day after discontinuing use of the other method
  - Start the first pack on any day of the week
  - Use additional nonhormonal contraception for **next 48 hours**
  - Unique considerations for switching from IUS after removal
- Concomitant use with other hormonal contraceptives or IUS is unnecessary

TRANSLATING EFFECTIVE AND SAFE USE OF NORGESTREL TABLET TO THE NONPRESCRIPTION SETTING

Ensuring Effectiveness in the Nonprescription Setting

To Achieve Optimal Efficacy:	Appropriate Action
Adherence	Take one tablet daily Take at the same time each day
	Take a delayed or missed tablet as soon as possible Continue with the next dose Take norgestrel tablets continuously (no break between packs)
	Use additional nonhormonal contraception for the **next 48 hours** if: 1. Tablets are taken 3 or more hours late or are missed 2. Vomiting or diarrhea occurs within 4 hours of tablet intake

Ensuring Safe Use in the Nonprescription Setting

Health Condition	Appropriate Action
Breast cancer	Deselect from norgestrel use
Abnormal vaginal bleeding	Consult HCP before AND during norgestrel use
Bleeding pattern alterations	Recognize the difference between bleeding that requires HCP evaluation vs. bleeding due to norgestrel use
Interacting drugs (such as UA)	Ask a doctor or pharmacist before use Follow instructions for use of back-up contraception

Additional Considerations for the Nonprescription Setting

Population or Condition	Appropriate Action
Current use of a hormonal contraceptive or IUS (IUD)	Discontinue use of the current method before initiating norgestrel use Follow instructions for switching to another contraceptive method
Adolescents	Demonstrate comprehension of key DFL messages Demonstrate ability to follow Directions for Use

Key Questions for the Nonprescription Setting

- Will individuals with breast cancer or other progestin-sensitive cancers correctly self-identify as ineligible for norgestrel?
- Will norgestrel users identify abnormal vaginal bleeding requiring healthcare provider intervention before AND during use?
- Will norgestrel users understand the risks associated with concomitant use of some drugs, particularly ulipristal?
- Will individuals understand how to switch from a prescription contraceptive to norgestrel without having an unintended pregnancy?

Summary

- Efficacy and safety of prescription norgestrel tablet established 1973
- Challenging to quantify effectiveness in the nonprescription setting
- Uncertainty whether users will adhere to dosing regimen
- Outstanding safety concerns in individuals with:
  1. Undiagnosed or history of breast or other progestin-sensitive cancer
  2. Abnormal vaginal bleeding of undiagnosed etiology
  3. Drug interactions, particularly with ulipristal emergency contraceptive use
- Use in adolescents presents unique concerns

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Consumer Behavior Studies (Label Comprehension, Targeted Breast Cancer Self-Selection, and Self-Selection in ACCESS)

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Center for Drug Evaluation and Research

May 9, 2023

Outline

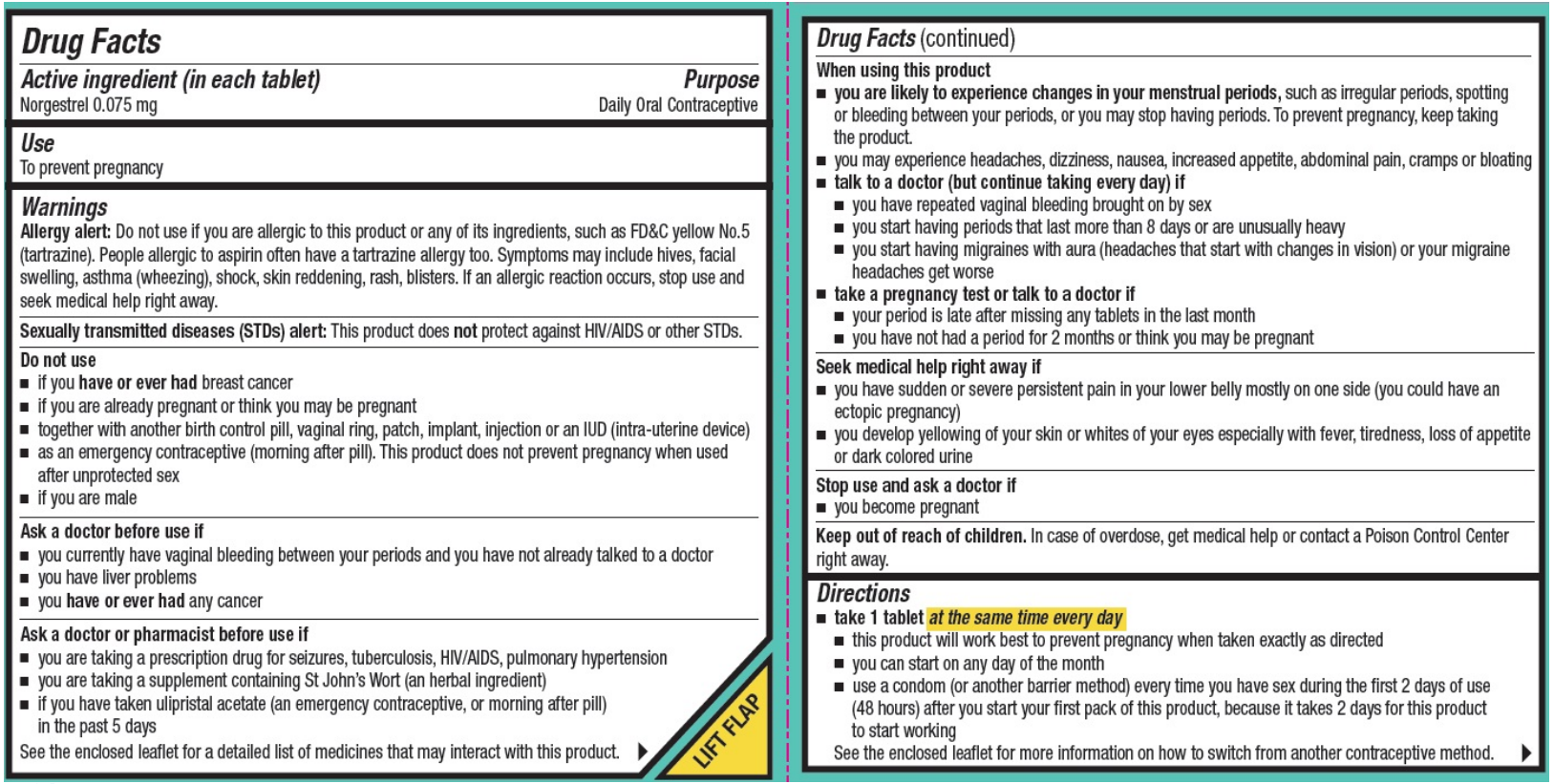
- Nonprescription Labeling
- Overview of Consumer Behavior Studies
- Pivotal Label Comprehension Studies
- Targeted Breast Cancer Self-Selection Study
- Self-Selection Component of Actual Use Study (ACCESS)
- Summary of Subgroups of Interest
- Conclusion

NONPRESCRIPTION LABELING

Nonprescription Labeling

- No gatekeeper - consumers must self-select and use on their own.
- Drug Facts Label (DFL) - all critical information necessary for safe and effective use
- DFL includes the following sections:
  - Warnings
  - When using this product
  - Stop use and ask a doctor if
  - Directions for use

Proposed Drug Facts Label (DFL Version H)



Drug Facts

Active ingredient (in each tablet)
Norgestrel 0.075 mg

Purpose
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)
- if 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.

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.

Proposed Drug Facts Label (DFL Version H)

continued

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 a 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

Nonprescription Labeling

- Consumer information leaflet (CIL) - supplementary use information
- Principal display panel (PDP) – outer box
- Blister pack- inner plastic packaging

Proposed Principal Display Panel

OVERVIEW OF CONSUMER STUDIES

Label Comprehension Study

- Foundational in nonprescription drug development
- Assess comprehension of important statements
- Typically “all comers”
- Minimum 30% limited literacy (LL)
- Participants read DFL, asked scenario questions about hypothetical consumers – “open book”
- Limitation: Understanding does not always translate to behavior

Targeted Self-Selection (Deselection) Study

- Assess whether consumers can apply understanding of the labeling to their own personal medical situation
- Typically utilized when concern about specific subpopulation (i.e. Do not use)
  - Adequate limited literacy representation
- Enrolls participants with medical condition(s) of concern
- Participants read DFL, are asked if it is appropriate for them personally to use given their personal health circumstances.
- Self-selection: Not tied to purchase intent, only their decision appropriateness to use

Actual Use Study (AUS)

- Simulates a nonprescription environment to assess whether a drug can be used properly, safely, and effectively in a "naturalistic" setting
- Deselection/self-selection phase (not always necessary to implement)
- Use phase – always implemented

Deselection/Self-Selection Phase of AUS

- All comers - typically widespread recruitment
- Consumers read DFL, asked if drug is appropriate for them to use based on their personal health history
- Primary objective usually correct deselection - among consumers with do not use (DNU) or ask a doctor before use conditions, how many adhere to labeling
- Secondary objective usually correct selection - among the self-selection population, how many people made a correct decision regarding product use

Deselection/Self-Selection/Use Phase of AUS

- All participants who say the product is medically appropriate to use are asked if they would like to purchase it
- Targeted medical history; those with contraindications are excluded from purchase
- Purchasers then enter the use phase of the trial

Use Phase of AUS

May assess:

- Adherence – taking the drug in accordance with the DFL
- Safety - adverse events (AEs) that occur during study
- Effectiveness – whether clinical benefit in prescription setting is reproduced in nonprescription setting

Consumer Behavior Study Thresholds

- Primary endpoints based on clinical importance
- Multiple endpoints designed as co-primary endpoints
  - Label comprehension endpoints typically 90%
  - Deselection endpoints typically 90%, selection endpoints 85%
  - Adherence endpoints typically 85%
- Endpoints assessed at the lower bound (LB) of the two-sided exact 95% confidence interval
  - Thresholds are targets, not hard pass/fail
  - Secondary, exploratory endpoints typically do not have thresholds

OVERVIEW OF NORGESTREL CONSUMER BEHAVIOR STUDIES

Overview of Norgestrel Consumer Behavior Studies

Study Type/name	Study Objectives	Study Design	Number of Participants
Pivotal DFL Label Comprehension	Evaluate comprehension of important DFL messages	Single visit, virtual interview	477 in LCS-only
CIL Label Comprehension	Evaluate comprehension of key CIL messages	Single visit, in person	551
Targeted Breast Cancer Self-Selection	Evaluate proposed labeling to guide correct deselection in females with breast cancer	Single visit, virtual	206 in self-selection cohort
Actual use – self-selection phase (ACCESS)	Evaluate proposed labeling to guide appropriate consumer deselection and selection	Single visit, in person (virtual during pandemic)	1772 in self-selection population
Actual use – use phase (ACCESS)	Evaluate proposed labeling to guide appropriate consumer use	Single arm, non-randomized, 24 week study	883 in user population

NORGESTREL PIVOTAL LABEL COMPREHENSION STUDIES

Pivotal DFL Label Comprehension Study (LCS)*

- Conducted among 477 females ages 11-50 with no history of breast cancer, 26% of limited literacy
- 14 primary endpoints with pre-specified target thresholds of 90%, 19 secondary endpoints, one other endpoint
- FDA reviewed verbatims to determine whether we agreed with coding of “correct” or “acceptable”
  - As a result, four primary endpoints recalculated, although none changed substantially; verbatim review revealed areas of confusion

*DFL evaluated for comprehension – earlier version (G) of proposed DFL (relatively minor differences)

Comprehension of Key DFL Statements About Adherence – Close to/Above 90% Threshold...

DFL Statement	Overall Correct % (LB)
Take one tablet every day	99 (**98,** 100)
Take one tablet at the same time every day	98 (**96,** 99**)**
Do not use together with another birth control, vaginal ring, patch, implant, injection, or IUD	94 (**90,** 96)
When you finish this pack, start the next one the following day without a break.	92 (**89,** 94)
If you are more than three 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,** 98)

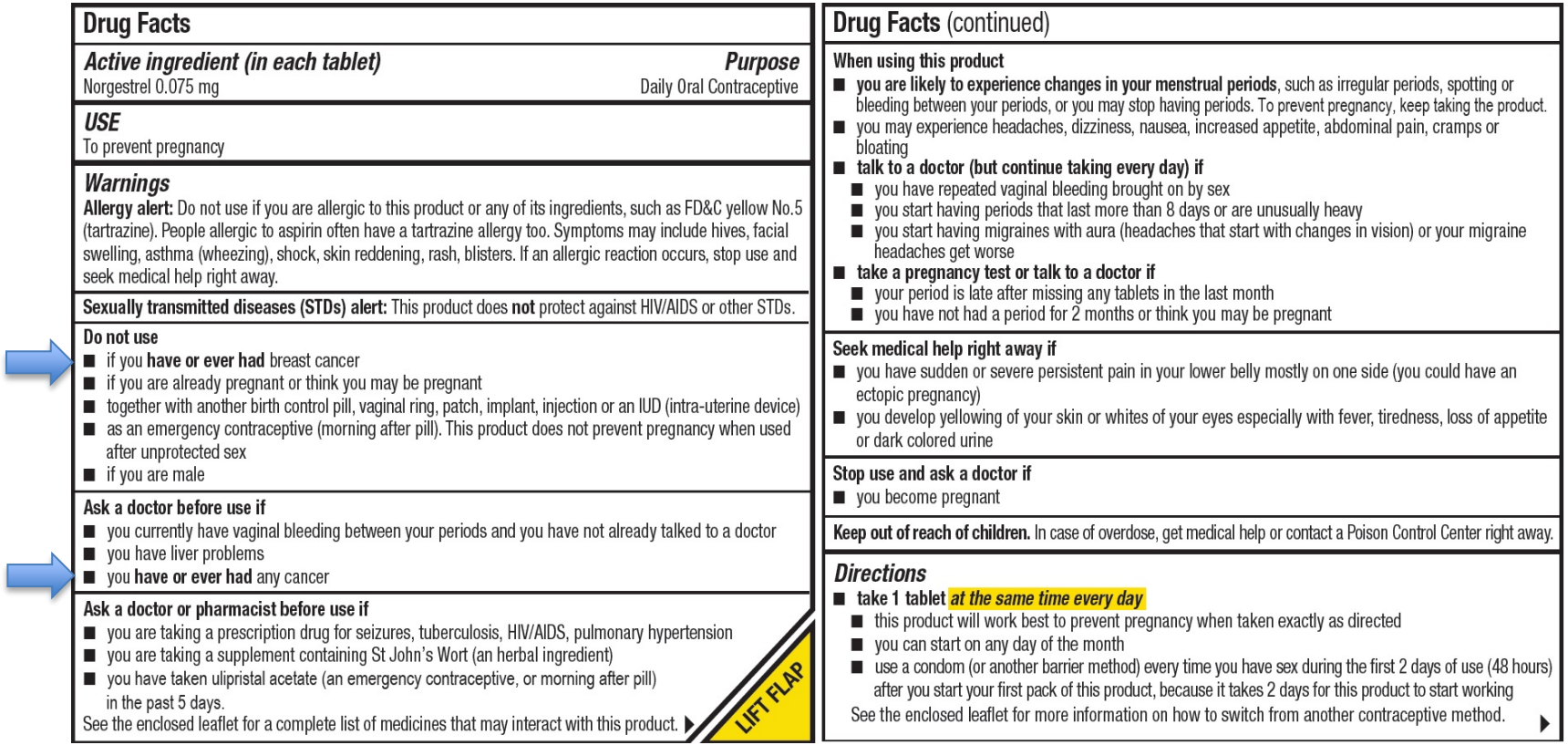
However, all DFL Statements About Need for Back-up Contraception Were Below 90% Threshold

DFL Statement – Use a condom or other barrier method every time…	Overall correct %
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	87 (**84**, 90)
You have sex for the next 2 days (48 hours) if you were 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	83 (**80**, 87)
You have sex for 2 days (48 hours) 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	85 (**82**, 88)

Comprehension of Key DFL Statements About Safe Use: Below 90% Threshold

DFL Statement	Overall Correct % (LB, UB)
Do not use if you have or ever had breast cancer • Confusion with other DFL statement to ask a doctor before use with any cancer	84 (**80**, 87) 79 (**75**, 84) for age 18+
Ask a doctor before use if you currently have vaginal bleeding between your periods and you have not already talked to a doctor • Confusion with other statements on the DFL about vaginal bleeding	86 (**83**, 89)
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	82 (**78,** 85)

Drug Facts Label - Label Comprehension and Targeted Self-Selection Studies



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

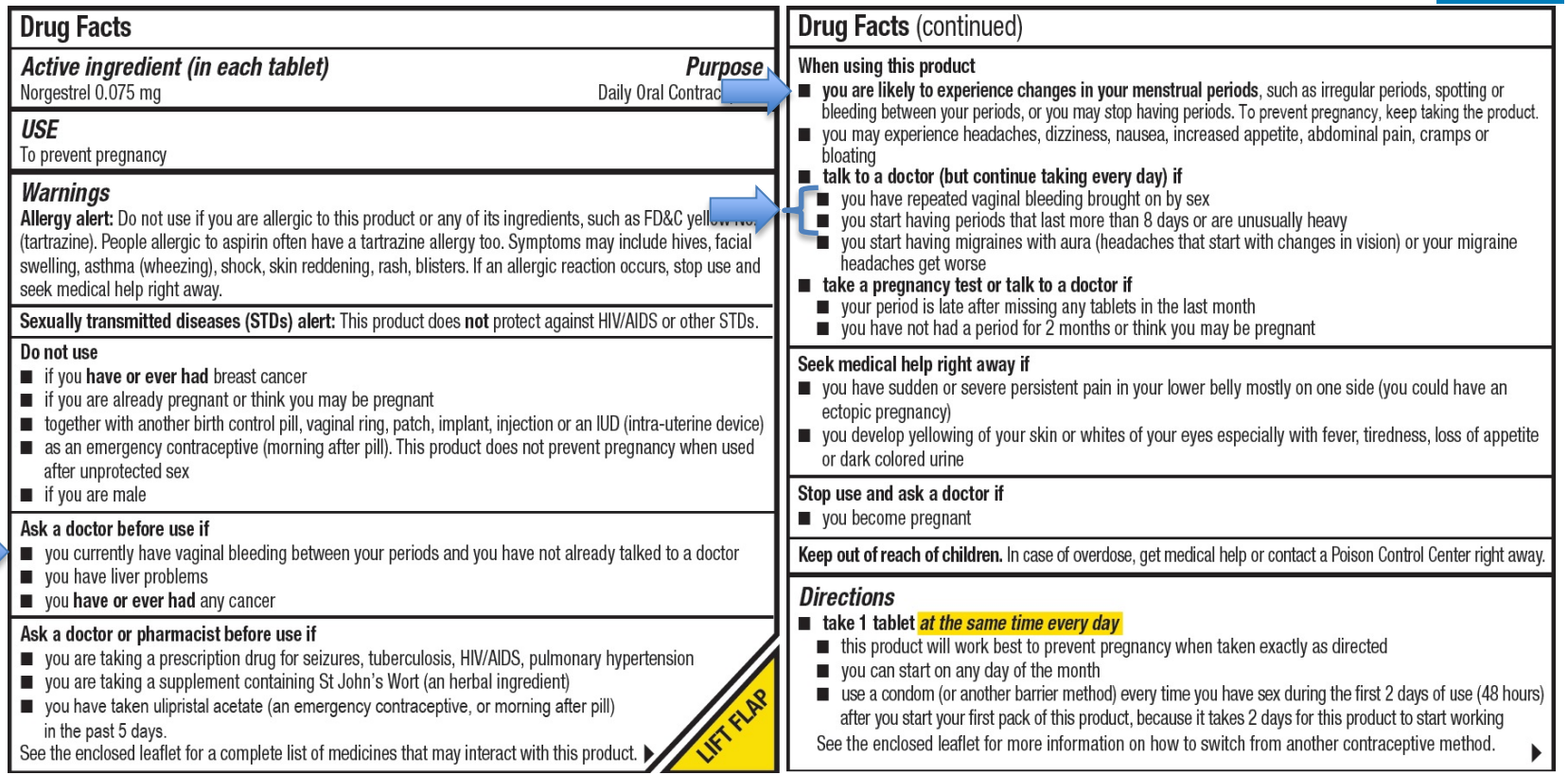
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

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 Label - Label Comprehension and Targeted Breast Cancer Self-Selection Studies



Drug Facts

Active ingredient (in each tablet) — ***Purpose***

Norgestrel 0.075 mg — Daily Oral Contrac

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 yell… (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.

Additional Consideration – Below 80% Threshold

DFL Statement	Overall correct % (LB, UB)
Do not use as an emergency contraceptive (morning after pill). This product does not prevent pregnancy when used after unprotected sex. • Confusion with other actions to be taken after missing a tablet	76 (**71**,79)

DFL LCS – Adolescent Comprehension (PE)*

DFL Statement	Ages 11-14 N=74	Ages 15-17 N=78	Ages 18+ N=325
When to use condom/barrier methods:			
• When first starting norgestrel	**80**	94	87
• After missing a dose	**66**	89	86
When you finish a pack, start the next one the following day without a break	**78**	96	94
Do not use as an emergency contraceptive (morning after pill)	**57**	**73**	**80**

*Point estimate

DFL LCS – Adolescent Comprehension (PE) (cont'd)

DFL Statement	Ages 11-14 N=74	Ages 15-17 N=78	Ages 18+ N=325
Ask a doctor or pharmacist before use if you have used an emergency contraceptive containing UA in past 5 days	**69**	80	85

DFL LCS – Limited Literacy (LL) Comprehension

- Do not use as an emergency contraceptive (morning after pill). This product does not prevent pregnancy when used after unprotected sex
  - Normal Literacy (NL) 81% PE vs LL **56%** PE
- When to use a condom or barrier method: If you are more than three hours late or miss taking your tablet on one or more days…
  - NL 88% PE vs LL **71%** PE
- 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
  - NL 85% PE vs LL **73%** PE

Consumer Information Leaflet Label Comprehension Study

- Objective – assess understanding of the Consumer Information Leaflet (CIL) (2017 version assessed)
- Conducted among 551 males and females ages 11+, 25% of limited literacy
- No primary endpoints; FDA does not agree
- Verbatim responses reviewed for Applicant's coding of "correct" or "acceptable"
  - Result - five endpoints had different results, but only one changed substantially

Most Important CIL Statements (Not Reinforced on DFL) Had Lower Comprehension

CIL Statement	Overall Correct % (LB, UB)
If you are switching from another birth control pill, vaginal ring, or patch, start taking Opill the day after you stop the other method Confusion with other directions on the CIL, citing a transition period of "two days" or "five days"	81 (**78**, 84)
What if I have taken an emergency contraceptive before starting Opill? Also, use a condom or other barrier method every time you have sex until your next period.	80 (**77**, 84)

CIL LCS: Comprehension of Adolescents

- What if I have taken another emergency contraceptive before starting Opill? Use a condom or another barrier method every time you have sex until your next period.
  - Age 18+ 87% PE, Adolescents **66%** PE

CIL LCS: Comprehension of Limited Literacy Subgroup

- 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
  - NL 86% PE, LL **66% PE**
- What if I have taken another emergency contraceptive before starting Opill? Use a condom or another barrier method every time you have sex until your next period.
  - NL 89% PE, LL **74% PE**

CIL LCS: Design and Interpretation Limitations

- No pre-specified thresholds for any endpoints.
- Placement and wording of some important messages in the tested version were subsequently revised but not retested
- Design and illustrations also revised
- Therefore, comprehension in this study may be of limited utility in assessing comprehension of current CIL

NORGESTREL TARGETED BREAST CANCER SELF-SELECTION STUDY

Targeted Breast Cancer Self-Selection Study

- Objective - evaluate the adequacy of the DFL in facilitating correct deselection by women with breast cancer (90% threshold for deselection)*
- Conducted among 206 females ages 18-50 with current or past history of breast cancer, 5% of limited literacy.
- Participants not informed as to the reason recruited
- Self-selection question: “Given what you have read on the label and your own health history, is this product okay or not for you personally to use?”

*Based on DFL version G, as with LCS

Targeted Breast Cancer Self-Selection Results – Threshold Achieved

- Applicant-reported correct deselection: 97%, 95%CI (94%, 99%)
  - Six participants incorrectly said it would be okay for them to use
  - Applicant determined a seventh participant who said it was okay was in fact okay to use
- FDA-analysis correct deselection: 95%, 95%CI (91%, 97%)
  - FDA reviewers did not agree with Applicant determination on seventh participant
  - Four additional participants who stated that they would need to “ask a doctor” classified as stating it was potentially appropriate to use, since they did not automatically deselect

Targeted Breast Cancer Self-Selection – Summary

- Many females with current or previous breast cancer may correctly deselect from taking norgestrel
- However, some will consider it appropriate to use; a 90% threshold means that some women with current or previous breast cancer (up to 10%) may not properly deselect
- The extent of this issue and the resulting implications are not clear, since:
  - Only 5% of the study population was of limited literacy; therefore, there are concerns about generalizability to a real world setting. Potentially in a study population of 30% limited literacy, deselection could be substantially below threshold

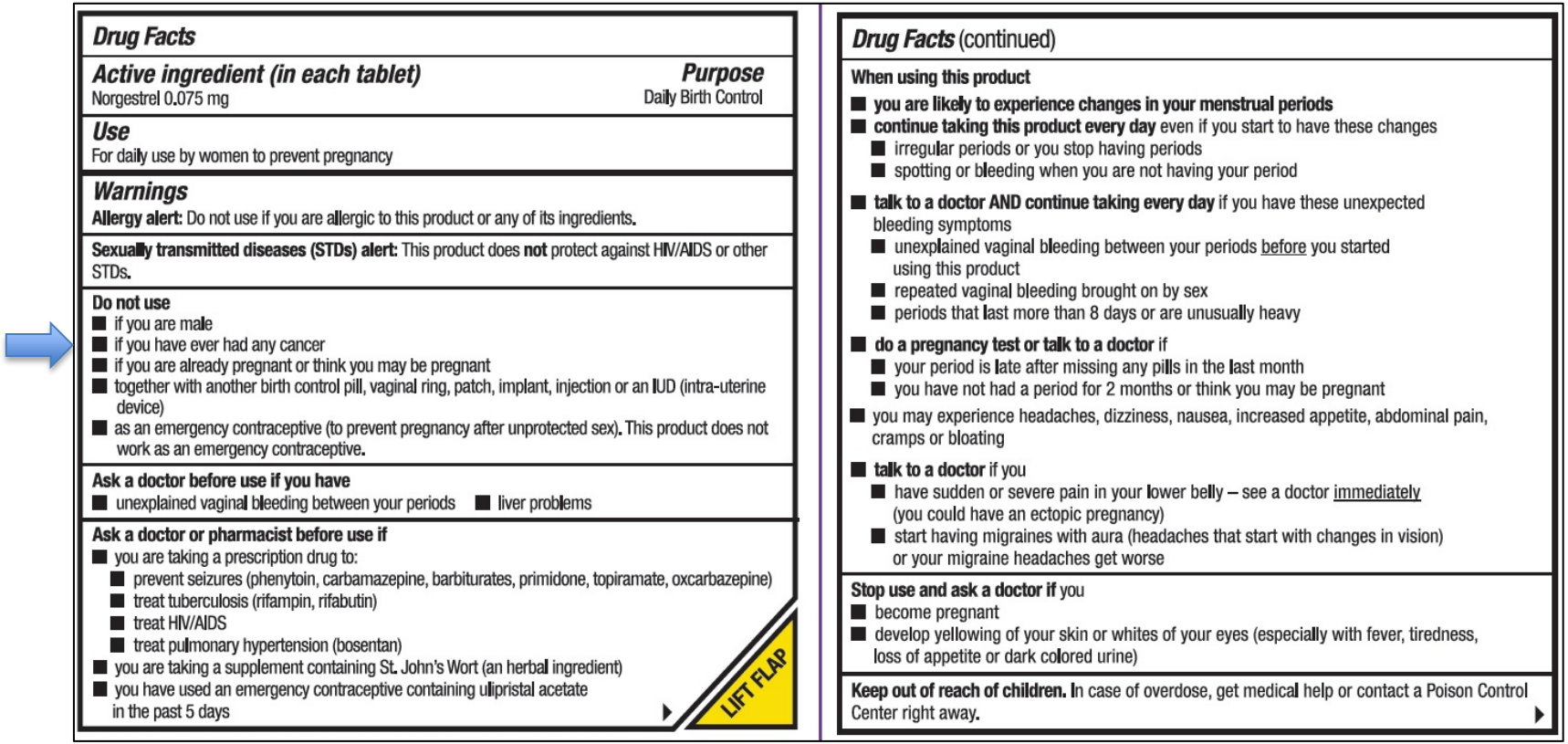
NORGESTREL ACCESS: SELF-SELECTION PHASE (SSP)

Overview ACCESS-SSP

Conducted among 1772 participants ages 11+ recruited through advertising for an interest in a new birth control product/new way to obtain birth control

- Primary objective per FDA - evaluate the adequacy of the DFL in facilitating correct deselection by women with medical conditions such as breast cancer and abnormal vaginal bleeding
  - Applicant declined to make this a primary endpoint
- Secondary objective - evaluate the adequacy of the DFL in facilitating correct self-selection (85% threshold for selection)
  - Applicant made this the primary endpoint
- LL representation was 13%
- Based on DFL version F (DNU for any cancer)

Drug Facts label Used in ACCESS (DFL Version F)



Drug Facts

Active ingredient (in each tablet) — **Purpose**
Norgestrel 0.075 mg — Daily Birth Control

Use
For daily use by women to prevent pregnancy

Warnings
Allergy alert: Do not use if you are allergic to this product or any of its ingredients.

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

Do not use
- if you are male
- if you have ever had any 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 (to prevent pregnancy after unprotected sex). This product does not work as an emergency contraceptive.

Ask a doctor before use if you have
- unexplained vaginal bleeding between your periods
- liver problems

Ask a doctor or pharmacist before use if
- you are taking a prescription drug to:
  - prevent seizures (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine)
  - treat tuberculosis (rifampin, rifabutin)
  - treat HIV/AIDS
  - treat pulmonary hypertension (bosentan)
- you are taking a supplement containing St. John's Wort (an herbal ingredient)
- you have used an emergency contraceptive containing ulipristal acetate in the past 5 days

LIFT FLAP

Drug Facts (continued)

When using this product
- **you are likely to experience changes in your menstrual periods**
- **continue taking this product every day** even if you start to have these changes
  - irregular periods or you stop having periods
  - spotting or bleeding when you are not having your period
- **talk to a doctor AND continue taking every day** if you have these unexpected bleeding symptoms
  - unexplained vaginal bleeding between your periods before you started using this product
  - repeated vaginal bleeding brought on by sex
  - periods that last more than 8 days or are unusually heavy
- **do a pregnancy test or talk to a doctor** if
  - your period is late after missing any pills in the last month
  - you have not had a period for 2 months or think you may be pregnant
- you may experience headaches, dizziness, nausea, increased appetite, abdominal pain, cramps or bloating
- **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)
  - start having migraines with aura (headaches that start with changes in vision) or your migraine headaches get worse

Stop use and ask a doctor if you
- become pregnant
- develop yellowing of your skin or whites of your eyes (especially with fever, tiredness, loss of appetite or dark colored urine)

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

ACCESS-SSP: Selection Questions

- 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?
  - (If yes) Tell me why you decided this medication is right for you to use if you were interested
  - (If no) Please tell me why you decided this medication is not right for you to use if you were interested
  - (If would talk to a doctor or pharmacist) Why would you want to talk to a doctor or pharmacist?
  - (If don't know) Can you tell me why you are uncertain?
- According to industry guidance on self-selection studies, assessment of selection decision is to be based on these questions, and not subsequent purchase questions, because purchase is influenced by many factors

ACCESS-SSP: Purchase Questions

- If answer to self-selection question is yes:
  - For pharmacy sites: Would you like to purchase Opill today to take home for your own use? It costs $10 for a one month supply or $20 for a three 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?
- If answer is no, please explain why not
- If answer is don't know, please explain why you are unsure

Selection vs Purchase

- Self-selection decision: 367/1772 participants (21%) stated that Opill was appropriate for them with their personal health history to use but did not want to purchase it, since:
  - They were already using a birth control product or
  - They didn't have a need for birth control
- Consistent with guidance for industry, FDA position is lack of purchase does not alter self-selection decision of the participant

ACCESS-SSP: Results – Correct Deselection

Correct deselection:

Numerator: # Participants who correctly decided that norgestrel was not medically appropriate

Denominator: Total # participants for whom use was not medically appropriate, according to DFL

- Applicant-reported correct deselection was 87% (95%CI: 75%, 92%)
  - This was already substantially below standard deselection threshold of 90%.
- FDA-analyzed correct deselection was 27% (95%CI: 18%, 37%)

ACCESS-SSP: Results – Correct Selection

Correct selection:

Numerator: # Participants who made the correct decision about whether it was medically appropriate or medically not appropriate to use

Denominator: # Participants in the study

Applicant-reported correct selection was 99%, 95%CI (98%, 100%)

- FDA-reported correct selection was 85%, 95%CI (83%, 87%)
  - This approaches the typical correct selection threshold of 85%

ACCESS-SSP: Results

- Difference in results mainly attributable to three factors:
  - Applicant's assessment based on purchase question
  - Applicant's post-hoc mitigation of some participants with cancer, unexplained vaginal bleeding, and liver disease as acceptable to use
  - Overall design led FDA to conservatively assess unexplained vaginal bleeding:
    - Lack of a study pathway for participants to follow the DFL and ask their doctor first
    - Lack of precise determination as to when participants talked to their doctors

ACCESS SSP – Participants with Cancer

- ACCESS based on earlier DFL*: Do not use if you have ever had any cancer (more restrictive than current DFL)
- 11 out of 14 stated it was potentially appropriate to use; three of these had potentially progestin sensitive cancer:
  - Two with breast cancer
    - One tried to purchase, had to be excluded from use phase
    - The other said she would talk to her pharmacist – did not automatically deselect
  - One with metastatic melanoma (tried to purchase, had to be excluded)

*DFL Version F

ACCESS SSP – Participants With Cancer

- Fourteen participants in the self-selection population self-reported cancer:
  - Breast cancer: 2
  - Metastatic melanoma in remission: 1
  - Thyroid and non-hodgkin lymphoma: 1
  - Thyroid: 3
  - Cervical cancer: 1
  - Cervical cancer and basal cell: 1
  - Colon cancer: 1
  - Skin cancer: 2
  - "Venereal": 1
  - Cervical dysplasia: 1

ACCESS SSP – Participants With Unexplained Vaginal Bleeding

- ACCESS based on earlier DFL*: Ask a doctor before use if you have unexplained vaginal bleeding between periods (current DFL adds: “and you have not already talked to a doctor)”
- During self-selection interview, 25 participants stated they had unexplained vaginal bleeding and that they had not spoken with a doctor about it
  - 17/25 failed to correctly deselect
  - 9 purchased product and continued into ACCESS-UP
  - Data on nature of bleeding issue was sparse in many instances
  - Study design issues
  - Therefore, FDA conservatively assessed all as inappropriate to use

*DFL version F

Access SSP – Adolescent Participants

Of 363 adolescents in the self-selection population:

- One adolescent, age 15, had cancer (thyroid) and correctly deselected
- Five (5) adolescents had unexplained vaginal bleeding; 1/5 correctly deselected
- Study not designed to systematically capture data on off-label usage; in a total of 50 study participants who stated at some point (either in self-selection or use) that they intended/were using off label, 27 were adolescents

ACCESS SSP – Limited Literacy Participants

- Three (3) participants with cancer were of LL; 1/3 correctly deselected
  - One of incorrect selectors had breast cancer and was of LL (tried to purchase)
- Four (4) participants with unexplained vaginal bleeding were of LL; 1/4 correctly deselected

(Cancer, Undiagnosed Vaginal Bleeding, Drug Interactions, Adolescents, and Limited Literacy)

SUMMARY OF LCS, TBCSS, AND ACCESS-SSP FOR SUBGROUPS OF INTEREST

Ensuring Safe Use in the Nonprescription Setting

Health Condition	Appropriate Action	Consumer Study Findings
Breast cancer	Deselect from norgestrel use	Mixed results: • LCS comprehension 80% • TBCSS met threshold but was not representative of LL population, and 7/206 failed to correctly deselect • In ACCESS, both breast cancer participants failed to correctly deselect

Ensuring Safe Use in the Nonprescription Setting

Health Condition	Appropriate Action	Consumer Study Findings
Vaginal bleeding. Bleeding pattern alterations	Consult HCP before AND during norgestrel use Recognize difference between bleeding that requires HCP evaluation vs bleeding due to norgestrel use	• LCS comprehension of ask a doctor before use 83%, confusion with other types of vaginal bleeding • In ACCESS, 17/25 (68%) participants with unexplained abnormal bleeding failed to correctly deselect
Interacting drugs (such as UA)	Ask a doctor or pharmacist before use Follow instructions for use of back-up contraception	• LCS comprehension of ask a doctor or pharmacist before use of UA 78%; need for back up contraception with UA 77%

Key Takeaways – Adolescent Comprehension/Appropriate Deselection

- Younger adolescents (ages 11-14) - low comprehension of important labeling messages such as:
  - Need for condoms or other barrier contraception when first starting the drug (80% PE)
  - Need for condoms or other barrier contraception after missing a dose (66% PE)
  - Start the next pack the day after you finish the last one (78% PE)
  - Ask a doctor or pharmacist before use if you have used an emergency contraceptive containing ulipristal acetate in past five days (69% PE)
- All adolescents demonstrated low comprehension of
  - Do not use as an emergency contraceptive (57% PE ages 11-14; 73% PE ages 15-17)
- Four of five adolescents did not correctly deselect for unexplained vaginal bleeding in ACCESS SSP
- Adolescent off-label use in ACCESS SSP

Key Takeaways – Comprehension and Appropriate Deselection in Individuals with Limited Literacy

- Inadequate understanding of:
  - Do not use as an emergency contraceptive (LL 56% PE vs NL 81% PE)
  - Use a condom or barrier method if you are more than three hours late taking your tablet or miss taking your tablet on one or more days (LL 71% PE vs NL 88% PE)
  - If you are switching from another birth control method, start taking Opill the day after you stop the other method (LL 66% PE vs NL 86% PE)
  - What if I have taken another emergency contraceptive before starting Opill? Use a condom or another barrier method every time you have sex until your next period. (LL 73% PE vs NL 85% PE)

Key Takeaways – Comprehension and Appropriate Deselection in Individuals With Limited Literacy (Cont'd)

- TBSSS had only 5% LL population
- ACCESS-SSP had only 13% LL population
- One out of three LL participants with cancer correctly deselected in ACCESS SSP
- One out of four LL participants with unexplained vaginal bleeding correctly deselected

Conclusions

- **Breast Cancer***:* Mixed results regarding comprehension, deselection
- **Unexplained Vaginal Bleeding**: Lower comprehension, deselection regarding need to ask a doctor before use
- **Overall correct selection:** proportion of total study participants who made a correct decision about appropriateness of use - approaches pre-specified threshold
- **Understanding of key DFL statements regarding effectiveness**: High comprehension of many key aspects of use but, including but not limited to LL and adolescent populations, lower comprehension of:
  - Need to use backup contraception when starting use and when late/missed a dose – these actions are critical to avoiding unintended pregnancy
  - Difference between norgestrel and emergency contraceptive
  - Need to ask a doctor or pharmacist before use after using an emergency contraceptive containing ulipristal acetate.

U.S. FOOD & DRUG ADMINISTRATION

Joint Meeting of the Nonprescription Drugs Advisory Committee and the Obstetrics, Reproductive, and Urologic Drugs Advisory Committee

NDA 017031 S-041 / Opill (norgestrel) tablet, 0.075 mg

ACCESS Study Use Phase: Design and Conduct

Jeena Jacob, MD, PharmD
Medical Officer
Division of Nonprescription Drugs II
Office of Nonprescription Drugs
Office of New Drugs
Center for Drug Evaluation and Research

May 9, 2023

Outline

- Actual Use Studies in Development Program
- ACCESS Study Design
- ACCESS Results
  - Improbable Dosing

Actual Use Studies in Development Program

- Applicant conducted two actual use studies
  - ACCESS (September 2019-August 2021)
  - OPTION (April-September 2018)
    - Planned 16-week study
    - Terminated early due to technical issues with the e-diary
    - None of the planned endpoints were analyzed

ACCESS Study Design

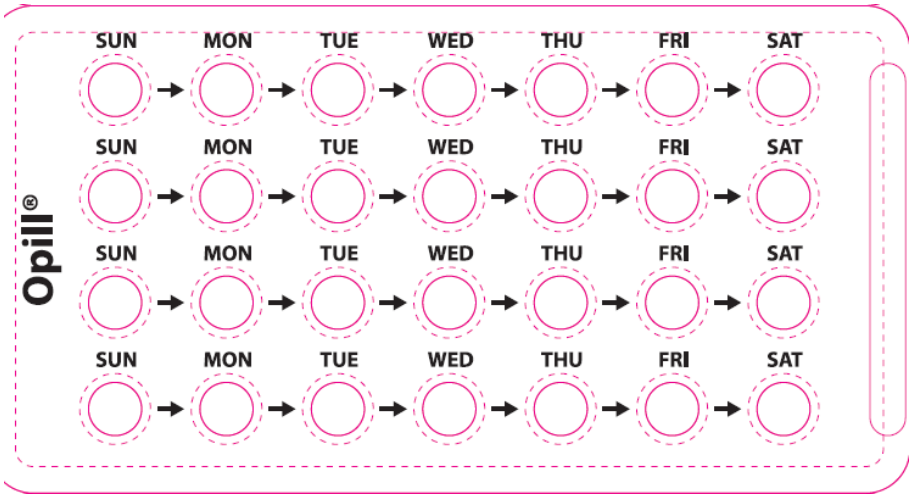
- Objective: Evaluate adequacy of nonprescription labeling to guide consumer use behavior
- Multi-center, 24-week, open-label, actual use study
- Inclusion Criteria
  - Female participants 11 years of age or older
- Exclusion Criteria
  - Males, premenarchal females, pregnancy, history of any cancer, known allergy to norgestrel or inactive ingredients

ACCESS Schedule of Events

	Enrollment visit/ first purchase	Weeks 2, 4, 8, 12, 16, 24	End of 24 weeks of use or earlier if early termination
Participant selection and purchase decision	x		
Collection of medical history, demographic information, administration of REALM (measure of literacy)	x		
Urine-based pregnancy test	x		
Scheduled follow-up telephone interviews		x	
Self-administered end-of-study pregnancy test			x
End-of-study telephone interview			x

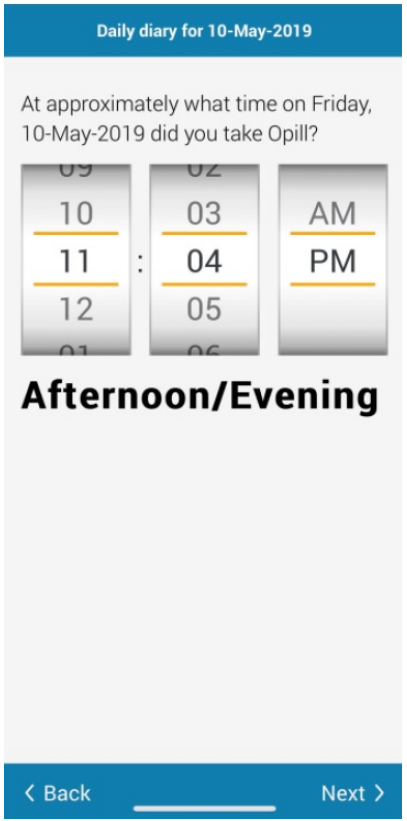
ACCESS Norgestrel Dispensing

- $10 for one 28-day package
- $20 for three 28-day packages
- Allowed to purchase up to eight packages during the study period
- Purchase to simulate naturalistic setting

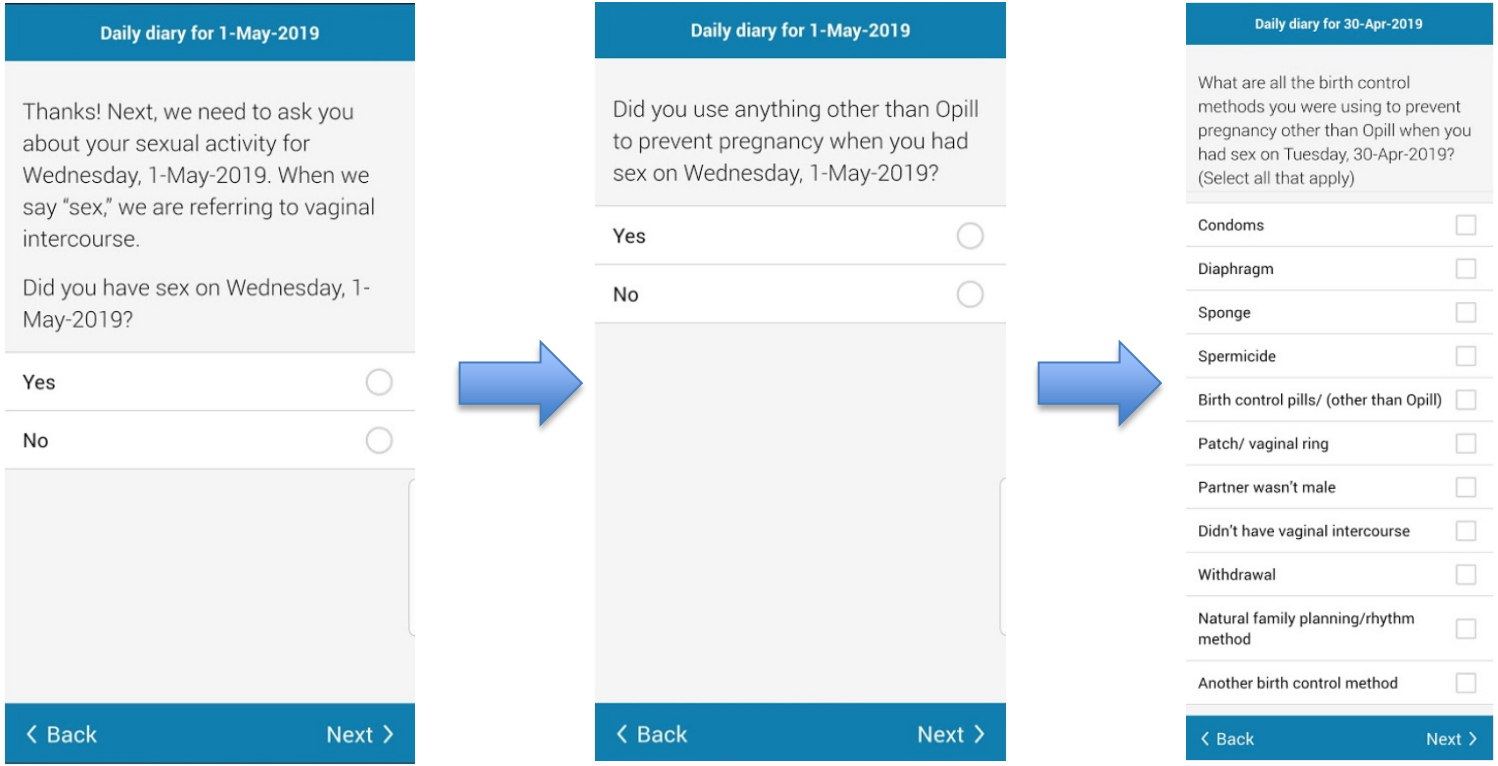


ACCESS E-Diary: Dosing

- Norgestrel use reported in online e-diary
- Reminder to complete e-diary every four days
- Data Entry
  - Indicate whether norgestrel taken
    - If yes:
      - Time tablet taken
      - Whether additional tablet taken (asked up to four times)
    - If no:
      - Why tablet not taken
      - If participant reported decision to discontinue norgestrel
        - » Reasons for discontinuation



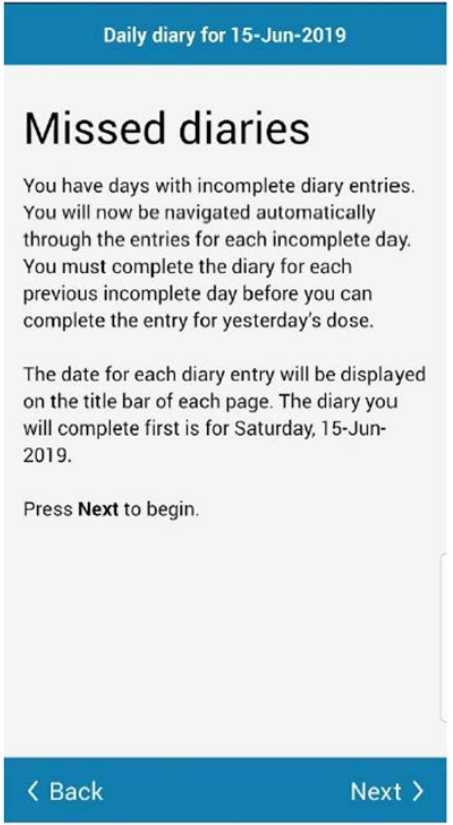
ACCESS E-Diary: Sexual Activity



*Questions only asked if participant is **18 years or older**

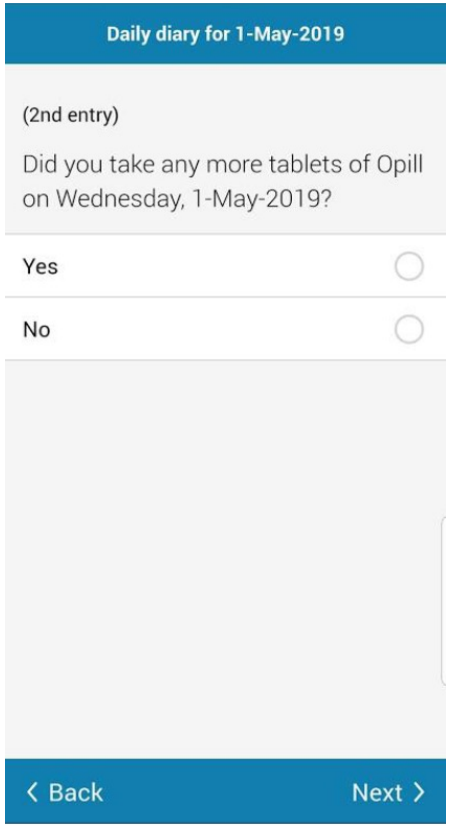
ACCESS E-Diary Issues

- Data entry retrospective, vulnerable to recall bias
  - E-diary data entry form not visible until next day
  - Participant allowed to enter previous dosing for up to ten days
    - Participants prompted to begin data entry at the oldest available incomplete date and complete diary until entry for current day



ACCESS E-Diary Issues

- Participants asked if they took an additional tablet up to four times each day



ACCESS Study Design Issues

- Participants paid for each day of completed diary
  - Could influence participants to make entry even if they could not recall their use that day
- Sexual activity not obtained in participants < 18 years old
  - Unknown how many at risk for pregnancy
- Study not designed for capture of timing and content of discussions with healthcare providers for all secondary endpoints
  - Limited interpretation of secondary endpoints and adherence to safety messages

ACCESS Primary Endpoints

Primary Endpoint	Endpoint Description
Primary Endpoint A: (Correct selection)	Proportion of participants who made correct selection decision
Primary Endpoint B: (Dosing-day daily use analysis)	Proportion of active use study days where participant reported taking the study drug in the e-diary
Primary Endpoint C: (Participant-level daily use analysis)	Proportion of participants who reported taking the study drug on ≥85% active use study days
Primary Endpoint D: (Time of day use analysis)	Proportion of active use study days with doses reported taken within three hours of time of the previous dose

ACCESS: Disposition

Study Conducted September 2019 - August 2021 at 36 sites
25 retail pharmacy sites, 10 women's health or adolescent clinics, single decentralized site for remote enrollment

Purchaser Population: Purchased/obtained norgestrel (N=955)	
Did not report use of norgestrel	72 (8%)
User Population: Reported use of norgestrel in the e-diary (N=883)	
Week 24 interim interview completed	471 (53%)
Withdrew from study	188 (21%)
Lost to follow-up	225 (25%)
End-of-study telephone interview completed	642 (73%)
End-of-study home pregnancy test results known	410 (46%)

ACCESS: Demographics of User Population

- Age
  - 23% participants < 18 years old
    - 6% participants 11-14 years old
      - Three 12 years old
      - None 11 years old
- Race
  - 30% Black or African American and 60% White
- Body Mass Index (BMI)
  - Mean BMI: 28
  - 23% overweight (BMI 25-29.9)
  - 35% obese (BMI ≥ 30)

ACCESS: Demographics of User Population

- History of hormonal birth control use
  - 72% had history of hormonal birth control use and 62% had a history of oral contraceptive use
- Literacy
  - 14% limited literacy
- Household income/education
  - 32% households with annual income <$25,000
  - 73% (participants 18+) not college graduates

Improbable Dosing

Total Tablets Reported Taken > Total Tablets Dispensed

Improbable Dosing

- Analysis Data Reviewer's Guide
  - Applicant reported deviation from SAP
    - Participants reported dosing earlier than dispensing date
    - Participants reported dosing after End-of-Study date
    - FDA queried:
      - How is it possible to report treatment start date that precedes dispensing date?
      - Clarify whether participants' total tablets reported taken > total tablets dispensed
      - Applicant confirmed that there were participants with reported tablets taken > tablets dispensed

Improbable Dosing

- 30% (261/883) of ACCESS User Population recorded improbable dosing
  - Improbable dosing= total # tablets reported taken > total # tablets dispensed
- Applicant conducted qualitative follow-up study (Improbable Dosing Follow-Up Study: (September 2022))
- Applicant submitted root-cause analysis at FDA's request (October 2022)

Improbable Dosing Follow-Up Study

Objective	Identify reasons participants reported taking more tablets than dispensed
Study Design	Qualitative Follow-Up Study
Date of Study	September 2022
Study Procedure	One-on-one interviews
Study Population	76/261 (29%) participants with improbable dosing agreed to participate

Improbable Dosing Follow-Up Study Results

- 49% (37/76) reported inadvertently reporting excess tablets
- 30% (23/76) reported having access to additional birth control that they were reporting on
  - 78% (18/23) reported receiving more norgestrel packs from the study site
  - 13% (3/23) reported receiving more norgestrel packs from another study participant
  - 9% (2/23) reported taking birth control other than norgestrel

Improbable Dosing Follow-Up Study Design Issues

- Recall bias
  - Time from ACCESS completion to Follow-Up Study ranged from 1-3 years
- Limited sample of improbable dosing cohort (29%;76/261)
- Lack of standardized format of questions
  - Potential for introduction of bias in questions

Conclusion: Study did not inform clear reason(s) for improbable dosing

Improbable Dosing: Root Cause Analysis

Root Causes Identified in Applicant's Submission	Description
Absence of design element for prevention of participant improbable dosing	
Study design did not have focus on identifying reported improbable dosing	a. Data collection and handling of data from sites, nurse interviewers, and e-diary were not focused on identifying improbable dosing b. Study plans did not have steps to identify improbable dosing
Issues related to set-up of the e-diary including the following	a. The participant could enter dosing data until e-diary deactivation. b. Participants received reminders to complete the e-diary until e-diary was deactivated (even though they may not have had drug available)

Improbable Dosing: Root Cause Analysis

- Populations disproportionately represented in improbable dosing group
  - Black or African American race, household income < $25,000, limited literacy, high school education level or less
- FDA Office of Scientific Investigations inspection findings
  - The audited data were verifiable against source data collected and recorded
  - The root cause of “improbable dosing” not discovered

Improbable Dosing: Conclusions

- A definitive root cause(s) not identified
  - Financial incentive as root cause of overreporting is speculative
- It is unknown whether:
  - Participants with improbable dosing **incorrectly used** norgestrel
  - **Incorrectly entered** use of norgestrel in e-diary
  - Other reasons
- Unclear whether ACCESS data can be relied upon
  - Study participants not part of improbable dosing group may also have incorrectly used or incorrectly reported, but may not have been identified with improper use because total tablets reported taken ≤ total tablets counted as dispensed

Improbable Dosing: Implications for Assessing Correct Use

- Large proportion of participants (30%) with improbable dosing major limitation in assessing correct use in ACCESS
- FDA analyses of adherence endpoints included
  - excluding data of participants with improbable dosing
  - classifying participants with improbable dosing as having reported incorrect use

U.S. FOOD & DRUG ADMINISTRATION

Joint Meeting of the Nonprescription Drugs Advisory Committee and the Obstetrics, Reproductive, and Urologic Drugs Advisory Committee

NDA 017031 S-041 / Opill (norgestrel) tablet, 0.075 mg

ACCESS Study Use Phase:
Use and Adherence Endpoints

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May 9, 2023

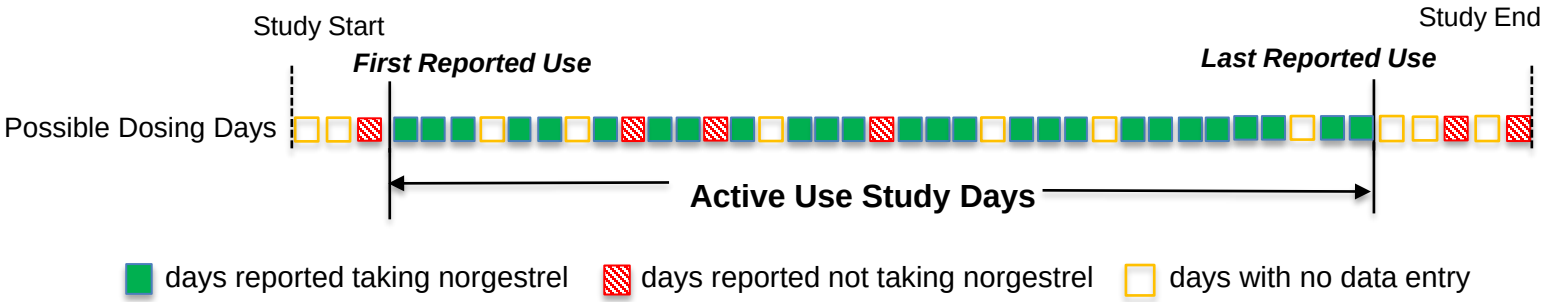
Outline

- Participants Disposition
- Basis of Adherence Analysis: Study Days
- Adherence Primary Endpoints
  - Taking One Tablet Every Day
  - Taking One Tablet at Same Time Every Day
- Sensitivity Analyses about Improbable Dosing
- Summary

ACCESS User Population

- A total of 883 participants reported using norgestrel at least once.
  - 470 (53%) completed 6 months of study and end of study interview
  - 225 (26%) lost to follow-up
  - 188 (21%) withdrew

Study Days



	Definition
Active Use Study Days (AUSDs)	**the study days between participant's first reported norgestrel use and last reported norgestrel use.**

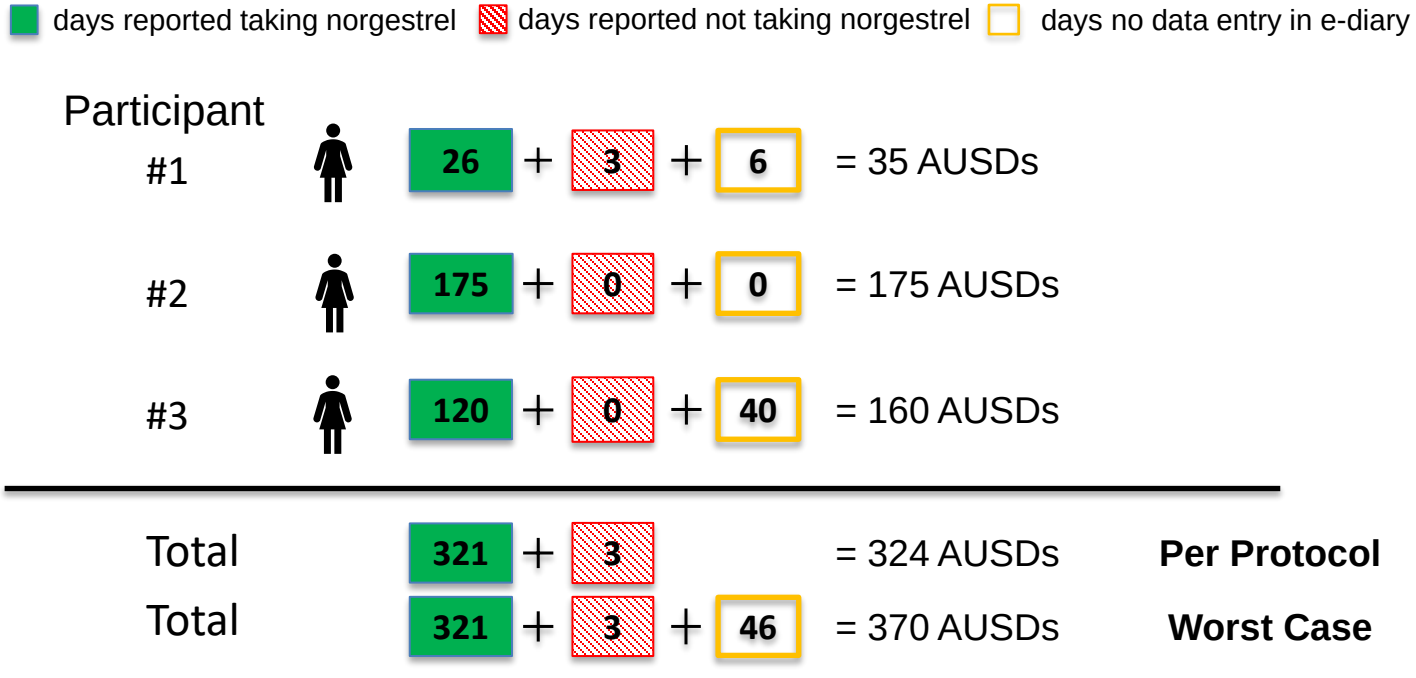
In the example, this participant had 35 AUSDs: 26 days reported taking norgestrel + 3 days reported not taking norgestrel + 6 days with no data entry in her e-diary.

The figure is based on Figure 8 in the ACCESS study report.

TAKING ONE TABLET EVERY DAY: PRIMARY ENDPOINTS B AND C

Dosing Day Analysis Example

Primary Endpoint B



Correct adherence (Per Protocol): 321/324 = 99%
Correct adherence (Worst Case) : 321/370 = 87%

Total Dosing Days for User Population (N=883)

	Study Days
Active Use Study Days (AUSDs)	96,437 (100%)
Days reported taking norgestrel	83,348 (86%)
Days reported not taking norgestrel	6,780 (7%)
Days no data entry in e-diary	6,309 (7%)

Note: when a participant reported multiple doses in one day, the multiple doses are considered as one AUSD, i.e., one study day taking norgestrel.

Participant Level Analysis Example

Primary Endpoint C

Participant					Taking norgestrel ≥ 85%		Adherence	
					Per Protocol	Worst Case	Per Protocol	Worst Case
#1	26	+ 3	+ 6	= 35 AUSDs	26/29=90%	26/35=74%		
#2	175	+ 0	+ 0	= 175 AUSDs	175/175=100%	175/175=100%		
#3	120	+ 0	+ 40	= 160 AUSDs	120/120=100%	120/160=75%		

Correct Adherence (≥ 85% Per Protocol) : 3/3 =100%
Correct Adherence (≥ 85% Worst Case) : 1/3 = 33%

days reported taking norgestrel | days reported not taking norgestrel | days with no data entry

taking norgestrel ≥ 85% use days | taking norgestrel < 85% use days

Participant Level Total Dosing Days

N=883 Participants	Mean(SD)	Median	Range [Min,Max]
Active Use Study Days (AUSDs) Per Participant	109 (57.8)	135	[1, 195]
Days reported taking norgestrel	94 (54.3)	93	[1, 195]
Days reported not taking norgestrel	8 (16.0)	1	[0, 146]
Days no data entry in e-diary	7 (16.1)	0	[0, 115]

Note: when a participant reported multiple doses in one day, the multiple doses are considered as one AUSD, i.e., one study day taking the product.

Definition: Primary Endpoints B and C

Primary Endpoint	Threshold	Analysis
B. Taking one tablet every day (Dosing day)	**85% LB**	**Per Protocol:** Numerator: # days reported taking the product Denominator: all AUSDs excluding days no data entry in e-diary **Worst Case (days no data entry imputed as not taking norgestrel)**
C. ≥85% dosing adherence (Participant level)	**85% LB**	**Per protocol:** Numerator: # participants who took the product on ≥85% of their AUSDs excluding days no data entry in e-diary Denominator: all participants **Worst Case (days no data entry imputed as not taking norgestrel)**

Abbreviations: AUSD, Active Use Study Days; LB, lower bound of the 95% confidence interval

Results: Primary Endpoints B and C

Primary Endpoint	Threshold	Analysis	Applicant's Analysis % Correct with 95% CI
B. Taking one tablet every day (Dosing Day)	85% LB	Per Protocol	93 (92, 93)
		Worst Case	86 (86, 87)
C. ≥85% dosing adherence (Participant Level)	85% LB	Per Protocol	85 (**82**, 87)
		Worst Case	72 (**68**, 74)

LB= lower bound of the 2-sided 95% confidence interval

TAKING ONE TABLE AT SAME TIME EVERY DAY PRIMARY ENDPOINTS D, D-1 AND D-2

Same time = dose taken ± 3 hours from time of previous dose

Days Included for Time of Dose

Days Included for Time of Dose	Active Use Study Days[1]		
	Days taking	Days not taking	Days no entry in e-diary
Applicant Analysis	✓	✗	Per Protocol: ✗ Worst Case: ✓[2]
FDA Analysis	✓	✓[2]	Per Protocol: ✗ Worst Case: ✓[2]

[1] start date for each participant excluded from days for time of dose; [2] days no entry in e-diary imputed as incorrect time of dose.

Definition: Primary Endpoints D, D-1, and D-2

Primary Endpoint	Threshold	Analysis
Applicant D. Taking one tablet at same time (Dosing Day)	**80% LB**	**Per Protocol** Numerator: # days same time Denominator: AUSDs excluding days not taking norgestrel and days no entry in e-diary **Worst Case (days no data entry imputed as incorrect time of dose)**

LB = lower bound of the 95% confidence interval, AUSDs = active use study days

- **FDA Primary Endpoint D-1:** Dosing Day Analysis same as D, except adding days reported not taking norgestrel into denominator
- **FDA Primary Endpoint D-2:** Participant Level Analysis based on D-1, proportion of participants who took norgestrel at same time ≥ 85% of days evaluable for time of dose

Results: Primary Endpoint D, D-1, and D-2

Primary Endpoint	Threshold	Analysis	% Correct with 95% CI
Applicant D. Taking one tablet at same time (Dosing Day)	80% LB	Per protocol	96 (96,96)
		Worst case	89 (89, 89)
FDA D-1. Taking one tablet at same time (Dosing Day)	80% LB	Per protocol	89 (88, 89)
		Worst case	83 (82, 83)
FDA D-2. ≥85% same time adherence (Participant Level)[1]	80% LB	Per protocol	74 (**71**, 77)
		Worst case	62 (**59**, 65)

LB= lower bound of the 95% confidence interval

[1]FDA primary endpoint D-2 was not specified in Applicant's protocol.

IMPROBABLE DOSING AND SENSITIVITY ANALYSES

Improbable Dosing and Sensitivity Analyses

- Improbable dosing: e-diary doses reported > doses dispensed
- 261 of 883 (30%) in User Population had improbable dosing
  - 32 exceeded over 100 doses, 2 exceeded over 500 doses, max 694
  - Actual use behavior in these participants unclear
- FDA analyses:
  - Excluding participants with improbable dosing
  - Classifying participants with improbable dosing as incorrect

Results – Primary Endpoints B and C

Primary Endpoint	Analysis	Applicant's Analysis	FDA Analysis: Excluding Participants with Improbable Dosing	FDA Analysis: Classifying Participants with Improbable Dosing as Incorrect
B. Taking one tablet every day (Dosing Day)	Per protocol	93 (92, 93)	92 (92, 92)	62 (**62**, 62)
	Worst case	86 (86, 87)	85 (85, 86)	58 (**58**, 58)
C. ≥85% dosing adherence (Participant Level)	Per protocol	85 (**82**, 87)	83 (**80**, 86)	59 (**55**, 62)
	Worst case	72 (**68**, 74)	70 (**66**, 73)	49 (**46**, 53)

- All results are % correct with 95% confidence interval
- Threshold for Primary endpoints B and C is 85% lower bound of 95% confidence interval.

Results – Primary Endpoints D, D-1, and D-2

Primary Endpoint	Analysis	All Participants	FDA Analysis: Excluding Participants with Improbable Dosing	FDA Analysis: Classifying Participants with Improbable Dosing as Incorrect
Applicant D. Taking one tablet at same time (Dosing day)	Per protocol	96 (96, 96)	95 (95, 95)	64 (**64**, 64)
	Worst case	89 (89, 89)	88 (88, 88)	59 (**59**, 60)
FDA D-1. Taking one tablet at same time (Dosing day)	Per protocol	89 (88, 89)	87 (87, 88)	59 (**59**, 59)
	Worst case	83 (82, 83)	81 (81, 82)	55 (**55**, 56)
FDA D-2. ≥85% same time adherence (Participant level)[1]	Per protocol	74 (**71**, 77)	72 (**68**, 76)	51 (**47**, 54)
	Worst case	62 (**59**, 65)	60 (**56**, 64)	42 (**39**, 45)

- All results are % correct with 95% confidence interval
- Threshold for Primary endpoints D-1, D-2 and D-3 is 80% lower bound of 95% confidence interval.

[1]FDA primary endpoint D-2 was not specified in Applicant's protocol.

ACCESS Use Phase: Summary

- Adherence analysis results for correct adherence, under different assumptions:
  - Taking one tablet every day: ranges **46% to 92%** lower bound
  - Taking one tablet at the same time every day: ranges **39% to 96%** lower bound

Conclusion

- Uncertainties about accuracy for e-diary reporting calls into question reliability of ACCESS User Phase data to assess adherence to instructions in the Drug Facts label necessary for pregnancy prevention:
  - Unclear if improbable dosing is incorrect use or incorrect e-diary entry, or other reasons
  - Large proportion of participants with improbable dosing (30%) raises concerns about accuracy of reporting among participants who did not report taking more tablets than dispensed.

U.S. FOOD & DRUG ADMINISTRATION

Joint Meeting of the Nonprescription Drugs Advisory Committee and the Obstetrics, Reproductive, and Urologic Drugs Advisory Committee

NDA 017031 S-041 / Opill (norgestrel) tablet, 0.075 mg

ACCESS Study Use Phase Secondary Endpoints and Safety Findings from Uncontrolled and Postmarketing Data

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Office of New Drugs
Center for Drug Evaluation and Research

May 9, 2023

Outline

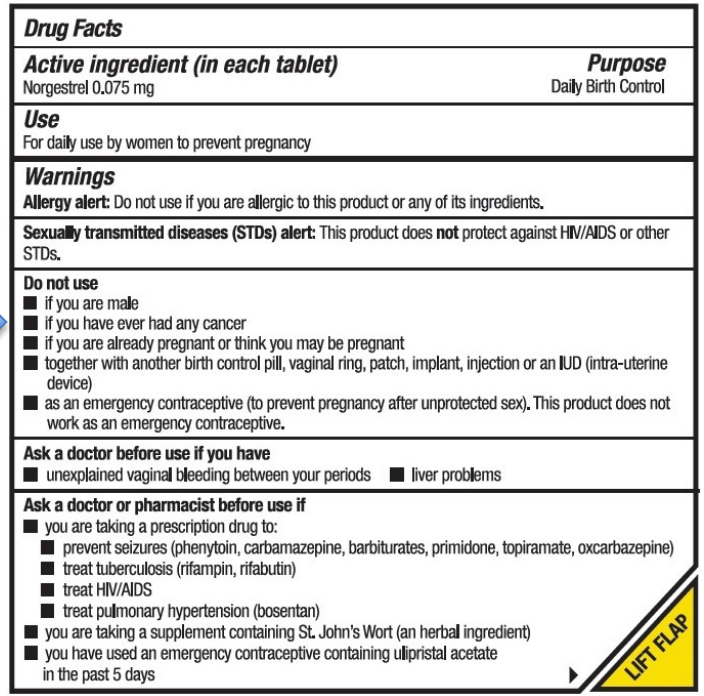
- ACCESS Study Secondary Endpoints
- ACCESS Study and Postmarket Safety
- Actual Use Conclusions

ACCESS STUDY USE PHASE SECONDARY ENDPOINTS

Changes Made to Proposed DFL After ACCESS AUS

- Cancer warning
  - DFL ACCESS:
    - Do not use “if you have ever had any cancer”
  - DFL sNDA:
    - Changed to do not use “if you have or ever had breast cancer”
    - “if you have or ever had any cancer” moved to ask a doctor or pharmacist before use section
  - May have affected self-selection phase

DFL Used in ACCESS (Version F)



Drug Facts

Active ingredient (in each tablet) — ***Purpose***
Norgestrel 0.075 mg — Daily Birth Control

Use
For daily use by women to prevent pregnancy

Warnings
Allergy alert: Do not use if you are allergic to this product or any of its ingredients.

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

Do not use
- if you are male
- if you have ever had any 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 (to prevent pregnancy after unprotected sex). This product does not work as an emergency contraceptive.

Ask a doctor before use if you have
- unexplained vaginal bleeding between your periods
- liver problems

Ask a doctor or pharmacist before use if
- you are taking a prescription drug to:
  - prevent seizures (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine)
  - treat tuberculosis (rifampin, rifabutin)
  - treat HIV/AIDS
  - treat pulmonary hypertension (bosentan)
- you are taking a supplement containing St. John’s Wort (an herbal ingredient)
- you have used an emergency contraceptive containing ulipristal acetate in the past 5 days

LIFT FLAP

ACCESS Use Phase: Secondary Endpoints

Secondary Endpoint	Endpoint Description
A	Self-selection endpoint (correct de-selection)
B through D	Adherence endpoints for mitigating behaviors (abstinence or use of condom or barrier protection in setting of a late or missed tablet)
E through O	Assess actions pertaining to use directions and safety-related messages on DFL
P	Pregnancies occurring on-treatment with norgestrel

ACCESS Secondary Endpoints: High Adherence to DFL Messages

Secondary Endpoint	Applicant's Analysis	FDA Analysis
F: participants who did not use norgestrel with another hormonal contraceptive or intrauterine device	99% (872/883)	Concur with Applicant

- Eleven participants reported concomitant use
  - 8/11 reported concomitant use at enrollment
  - 3/11 initiated use after enrollment
  - 10/11 had normal literacy
  - 5/11 were adolescents

ACCESS Secondary Endpoints: High Adherence to DFL Messages

Secondary Endpoint	Applicant Analysis	FDA Analysis
I: correct follow-up action[1] for pregnancy	100% (6/6)[2,3]	80% (8/10)[2,3]

1- Correct follow-up action**:** speaking with a healthcare provider during the study and stopping use of norgestrel within three days of finding out they were pregnant
2- All participants classified as becoming pregnant pre-treatment or on-treatment were included in the denominator for this endpoint
3- FDA analysis classified 10 participants as becoming pregnant pre-treatment or on-treatment while the Applicant classified 6 participants as becoming pregnant pre-treatment or on-treatment

ACCESS Secondary Endpoints: Low Adherence to DFL Messages

Secondary Endpoint	Applicant Analysis	FDA Analysis
K: late or missed period	71% (41/58)[1]	71% (41/58)[2]

1- Applicant Analysis: Classifies as correct all participants who either stopped use of the study drug, spoke to a healthcare provider, or took a pregnancy test
2- FDA Analysis: Classifies as correct participants who spoke to a healthcare provider about late or missed periods or took a pregnancy test

ACCESS Secondary Endpoints: Low Adherence to DFL Messages

Secondary Endpoint	Applicant Analysis[1]	FDA Analysis[2]
L: unusually heavy periods or periods that last more than eight days	71% (32/45)	18% (9/50)
M: vaginal bleeding brought on by sexual intercourse	50% (1/2)	0% (0/2)

1- Applicant Analysis: Classifies all participants as correct who stopped study drug or consulted a healthcare provider for any reason at any time during the study. This analysis only includes participants who completed the end-of-study interview.

2- FDA Analysis: Classifies participants as correct who consulted a healthcare provider about specified symptoms (heavy periods or periods that last more than eight days or vaginal bleeding brought on by sexual intercourse). Analysis includes all participants who reported these symptoms and not only those who completed the end-of-study interview.

ACCESS Secondary Endpoints: Low Adherence to DFL Messages

Secondary Endpoint	Applicant Analysis[1]	FDA Analysis[2]
J: sudden or severe abdominal pain	67% (6/9)	33% (3/9)
N: new migraines with aura or migraines that got worse	78% (7/9)	46% (5/11)

1- Applicant Analysis: Classifies participants as correct who spoke to a healthcare provider for any reason at any time during study and only includes participants who completed the end-of-study interview

2- FDA Analysis: Classifies participants as correct who spoke to a healthcare provider about condition (abdominal pain / migraine) and includes all participants who reported the condition (not only those who completed end-of-study interview)

ACCESS Secondary Endpoints: Results With High Level of Uncertainty

Secondary Endpoint	Applicant Analysis	FDA Analysis
E: pack transitions without a break between packs	92% (2,057/2,229)	86% (2,057/2,397)
G: use of barrier method or abstinence when initiating therapy	80% (543/681)	62% (543/883)
H: adherence to drug interaction warning	55% (11/20)	10% (2/20)
O: yellowing of the skin or whites of the eyes	Unable to be assessed: zero participants with these symptoms	
P: pregnancies that occurred on-treatment	55% (6/11)	82% (9/11)

ACCESS Secondary Endpoints: Results With High Level of Uncertainty

Secondary Endpoint	Analysis	Applicant's Result (% Correct with 95% CI	FDA's Sensitivity Analysis: Classifies Participants with Improbable Dosing as Incorrect (% Correct with 95% CI)
B: (Days on which tablet taken or participant reported mitigating behavior when no tablet was taken)	Per-Protocol	97 (97, 97)	66 (66, 66)
	Worst-Case	91 (91,91)	61 (61, 62)
C: (Participants who reported ≥ 85% adherence or mitigating behavior when no tablet was taken)	Per-Protocol	95 (93, 96)	67 (63, 70)
	Worst-Case	80 (77, 82)	55 (52, 59)
D: (Proportion of days on which tablet taken within 27 hours of the previous dose or reported mitigating behavior when tablet not taken within 27 hours of previous dose)	Per-Protocol	99 (99, 99)	66 (66, 67)
	Worst-Case	89 (89,90)	60 (59, 60)

Mitigating behavior: using a condom (or another barrier method) for any act of intercourse or abstaining from intercourse for the following two calendar days. Worst-case analysis: classifies all days with days with no entry in e-diary as incorrect

Abnormal Vaginal Bleeding of Undiagnosed Etiology

- 34 participants reported unexplained vaginal bleeding between periods prior to Use Phase
  - 27% (9/34) did not report speaking to a healthcare provider before use of the product

Off-Label Use

- Participants asked why they used norgestrel at the end-of-study interview
- Of 24 participants reporting off-label use:
  - 83% (20) normal literacy
  - 83% (20) less than 18 years old
    - 70% (14/20) in the 12-14 years old age group
  - 54% (13) regulate menstrual cycles
  - 38% (9) treat menstrual symptoms
  - 13% (3) treat acne
- Possible that off-label use may have occurred among other participants

Summary of Secondary Endpoints

- High adherence to DFL messages
  - Correct follow-up action for pregnancy
  - Do not use together with another hormonal contraceptive
- Low adherence to DFL messages
  - Sudden or severe abdominal pain
  - New migraines with aura or migraines that got worse
  - Late or missed period
  - Unusually heavy periods or periods that last more than eight days

Summary of Secondary Endpoints

- Results with high level of uncertainty
  - Pregnancies while taking norgestrel
  - Proportion of pack transitions where participant did not break between packs
  - Repeated vaginal bleeding brought on by sexual intercourse
  - Yellowing of the skin or whites of eyes
  - Proportion of participants taking one of the drugs listed in “ask a doctor or pharmacist before use” section and completed the correct action
  - Proportion of participants using barrier method or abstained from intercourse when initiating therapy
  - Adherence accounting for mitigating behaviors
    - With LB as low as 52% depending on assumptions regarding Improbable Dosing

ACCESS STUDY AND POSTMARKET SAFETY DATA

ACCESS: Safety Population

- Applicant's Safety Population (n=955)
  - All participants with signed informed consent
- FDA's Safety Population (n=883)
  - All participants reporting norgestrel use in e-diary
  - Same as User Population

ACCESS: Adverse Events

- No deaths
- Serious Adverse Events
  - 11 pregnancies in User Population; FDA classified 9 as on-treatment
  - 3 non-pregnancy serious adverse events unlikely to be drug-related
  - 1 thromboembolic event; causal link cannot be excluded
- Discontinuations due to adverse events
  - 7% (64/883) due to adverse events
    - Approximately half discontinued due to bleeding irregularities
- Adverse events in ACCESS consistent with prescription labeling
- Most common adverse events were bleeding irregularities

Postmarketing Data

- Data sourced from FDA databases, WHO, American Association of Poison Control Centers, Applicant's safety database, literature review
- Limitations
  - Spontaneous reporting, unknown denominator of cases, incomplete data, reporting bias
- Contribution to Safety Assessment
  - No conclusive data on specific safety concerns

ACTUAL USE CONCLUSIONS

ACCESS: Conclusions

- Study population
  - Magnitude of improbable dosing (30%) raises concerns about reliability of evidence of adherence
  - Root cause(s) of improbable dosing unknown
- Adolescents
  - Limited representation of younger adolescents
  - Sexual activity and risk for pregnancy unknown
  - Incorrect use potentially higher in adolescents
    - About 50% (5/11) participants reporting concomitant use of another hormonal contraceptive were adolescents
    - 20/24 participants who reported off-label use were adolescents

ACCESS: Conclusions

- Limited literacy
  - Greater proportion of improbable dosing in limited literacy group raises concerns regarding adequacy of evidence of adherence in this population
  - Low proportion of participants with limited literacy limits generalizability of findings to consumer population
- Unexplained vaginal bleeding
  - Approximately 25% with unexplained vaginal bleeding did not report speaking to a healthcare provider before use of norgestrel

U.S. FOOD & DRUG ADMINISTRATION

Joint Meeting of the Nonprescription Drugs Advisory Committee and the Obstetrics, Reproductive, and Urologic Drugs Advisory Committee

NDA 017031 S-041 / Opill (norgestrel) tablet, 0.075 mg

Summary

Pamela Horn, MD
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Division of Nonprescription Drugs II
Office of Nonprescription Drugs
Office of New Drugs
Center for Drug Evaluation and Research

May 9, 2023

Effectiveness in Nonprescription Setting

- Efficacy of product established in original NDA application and approved for marketing since 1973
  - Estimated likelihood of becoming pregnant during one year of use is around 2% in prescription setting
- Proposed indication and target population unchanged from prescription product

Effectiveness in Nonprescription Setting

- Applicant submitted:
  - ACCESS study
    - Pregnancy outcome data
    - Self-reported e-diary use data
    - Data on adherence to drug interaction “ask a doctor or pharmacist before use” (AADPBU) message
  - DFL Label Comprehension Study and CIL Label Comprehension Study
    - Use statements comprehension data

Effectiveness in Nonprescription Setting

Supportive Evidence	Evidence not Supportive	Uncertainties
Comprehension of directions for use	Comprehension of emergency contraception statement, including in adolescents and limited literacy subpops	Risk of pregnancy in adolescent ACCESS participants
Estimated likelihood of becoming pregnant during one year of use is 2-6% from ACCESS	Comprehension of when to use backup methods of contraception statements, including in adolescents and limited literacy subpops	Actual use in limited literacy population
	Comprehension of AADPBU drug interactions that could decrease norgestrel effectiveness	Reliability of e-diary adherence data
		Pregnancy test results for over half of ACCESS participants
		Adherence to drug interaction AADPBU in ACCESS

Safety in Nonprescription Setting

- Safety of product established in original NDA application and approved for marketing since 1973

- Proposed indication and target population unchanged from prescription product

Safety in Nonprescription Setting

- Applicant submitted:
  - ACCESS study
    - SS data
    - Self-reported e-diary use data
    - Adverse event data
  - TBCSSS (Targeted Breast Cancer Self-Selection Study)
    - SS data in participants with breast cancer
  - DFL Label Comprehension Study and CIL Label Comprehension Study
    - Safety statements comprehension data

Safety in Nonprescription Setting

- Progestin-sensitive cancer
  - TBCSSS supportive of correct deselection
  - LCS comprehension and incorrect deselection in ACCESS not supportive
- Abnormal vaginal bleeding of undiagnosed etiology
  - Comprehension of AADBU, incorrect deselection, and failure to seek care in ACCESS not supportive
- Use with another hormonal contraceptive comprehension and adherence of DNU DFL overall supportive
- Adolescents
  - Uncertainties with bone health risks and off-label use
- Limited literacy
  - Uncertainties remain for actual use and correct deselection due to underrepresentation

Conclusions

- Evidence of likelihood of effectiveness in nonprescription setting is mixed and limited
  - Uncertain reliability of actual use data assessing adherence to instructions in DFL necessary for pregnancy prevention
- Evidence of likelihood of appropriate deselection in consumers with
  - Progestin-sensitive cancer is mixed
  - Abnormal vaginal bleeding of undiagnosed etiology is not supportive
- Uncertainties in likelihood of safe and effective use are especially pronounced for adolescents and limited literacy subpopulations


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