

Norgestrel for nonprescription contraception: What you and your patients need to know

Scheduled to be available in 2024, Opill is the first hormonal birth control pill that has been approved for purchase OTC without a prescription. Here, how it works and where patients can get more information if they decide to use it.

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On July 13, 2023, the US Food and Drug Administration (FDA) approved norgestrel 0.075 mg (Opill, HRA Pharma, Paris, France) as the first non-prescription oral contraceptive pill (FIGURE). This progestin-only pill was originally FDA approved in 1973, with prescription required, and was available as Ovrette until 2005, when product distribution ceased for marketing reasons and not for safety or effectiveness concerns.¹ In recent years, studies have been conducted to support converted approval from prescription to nonprescription to increase access to safe and effective contraception. Overall, norgestrel is more effective than other currently available nonprescription contraceptive options when used as directed, and widespread accessibility to this method has the potential to decrease the risk of unintended pregnancies. This product is expected to be available in drugstores, convenience stores, grocery stores, and online in 2024.

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Dr. Chen reports being a speaker for Mayne Pharma. Dr. Yazdani-Sabouni reports no financial relationships relevant to this article.

doi: 10.12788/obgm.0335

How it works

The indication for norgestrel 0.075 mg is pregnancy prevention in people with the capacity to become pregnant; this product is not intended for emergency contraception. Norgestrel is a racemic mixture of 2 isomers, of which only levonorgestrel is bioactive. The mechanism of action for contraception is primarily through cervical mucus thickening, which inhibits sperm movement through the cervix. About 50% of users also have an additional contraceptive effect of ovulation suppression.²

Instructions for use. In the package label, users are instructed to take the norgestrel 0.075 mg pill daily, preferably at the same time each day and no more than 3 hours from the time taken on the previous day. This method can be started on any day of the cycle, and backup contraception (a barrier method) should be used for the first 48 hours after starting the method if it has been more than 5 days since menstrual bleeding started.³ Product instructions indicate that, if users miss a dose, they should take the next dose as soon as possible. If a pill is taken 3 hours or more later than the usual time, they should take a pill immediately and then resume the next pill at the usual time. In addition, backup contraception is recommended for 48 hours.²

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Based on the Centers for Disease Control and Prevention (CDC) Selected Practice Recommendations for Contraceptive Use, no examinations or tests are required prior to initiation of progestin-only pills for safe and effective use.³

Efficacy

The product label indicates that the pregnancy rate is approximately 2 per 100 women-years based on over 21,000 28-day exposure cycles from 8 US clinical studies.² In a recent review by Glasier and colleagues, the authors identified 13 trials that assessed the efficacy of the norgestrel 0.075 mg pill, all published several decades ago.⁴ Given that breastfeeding can have contraceptive impact through ovulation inhibition, studies that included breastfeeding participants were evaluated separately. Six studies without breastfeeding participants included 3,184 women who provided more than 35,000 months of use. The overall failure rates ranged from 0 to 2.4 per hundred woman-years with typical use; an aggregate Pearl Index was calculated to be 2.2 based on the total numbers of pregnancies and cycles. The remaining 7 studies included individuals who were breastfeeding for at least part of their study participation. These studies included 5,445 women, and the 12-month life table cumulative pregnancy rates in this group ranged from 0.0% to 3.4%. This review noted that the available studies are limited by incomplete descriptions of study participant information and differences in reporting of failure rates; however, the overall data support the effectiveness of the norgestrel 0.075 mg pill for pregnancy prevention.

Norgestrel’s mechanism of action on ovarian activity and cervical mucus

More recently, a prospective, multicenter randomized, crossover study was performed to better understand this pill’s impact on cervical mucus and ovulation during preparation for nonprescription approval. In this study, participants were evaluated with

frequent transvaginal ultrasonography, cervical mucus, and blood assessments (including levels of follicular-stimulating hormone, luteinizing hormone, progesterone, and estradiol) for three 28-day cycles. Cervical mucus was scored on a modified Insler scale to indicate if the mucus was favorable (Insler score ≥ 9), intermediate (Insler score 5-8), or unfavorable to fertility (Insler score ≤ 4).⁵

In the first cycle, participants were instructed to use the pills as prescribed (described as “correct use”). During this cycle, most participants (n = 34/51; 67%) did not ovulate, confirming that norgestrel 0.075 mg does impact ovulation.⁶ Most participants also had unfavorable cervical mucus (n = 39/51; 76%).⁶ Overall, 94% had full protection against pregnancy, either through lack of ovulation (n = 9), unfavorable mucus (n = 14), or both (n = 25). The remaining 3 participants ovulated and had intermediate mucus scores; ultimately, these participants were considered to have medium protection against pregnancy.^{7,8} (See the contraceptive protection algorithm [TABLE, page E13]).⁸

In the second and third cycles, the investigators evaluated ovulation and cervical mucus changes in the setting of either a delayed (by 6 hours) or missed dose mid-cycle.⁸ Of the 46 participants with evaluable data during the intervention cycles, 32 (70%) did not ovulate in each of the delayed- and missed-dose cycles. Most participants (n = 27; 59%) also demonstrated unfavorable mucus scores (modified Insler score ≤ 4) over the entire cycle despite delaying or missing a pill. There was no significant change to the cervical mucus score when comparing the scores on the days before, during, and after the delayed or missed pills (P = .26), nor when comparing between delayed pill use and missed pill use (P = .45). With the delayed pill intervention, 4 (9%) had reduced contraceptive protection (ie, medium protection) based on ovulation with intermediate mucus scores. With the missed pill intervention, 5 (11%) had reduced protection, of whom 3 had medium protection and 2 had minimum protection with ovulation and favorable mucus scores. Overall, this

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CDC contraception guidelines require no tests or clinical examinations prior to initiating progestin-only pills for safe and effective use

TABLE Contraceptive protection algorithm based on ovulation and cervical mucus scores⁸

		Ovarian status		
		No ovulation	Ovulation with abnormal luteal phase	Ovulation with normal luteal phase
Cervical mucus score	Unfavorable (Modified Inslar score 0-4)	Maximum	Maximum	Maximum
	Intermediate (Modified Inslar score 5-8)	Maximum	Medium	Medium
	Favorable (Modified Inslar score 9-12)	Maximum	Medium	Minimum

study shows that delaying or missing one pill may not impact contraceptive efficacy as much as previously thought given the strict 3-hour window for progestin-only pills. However, these findings are theoretical as information about pregnancy outcomes with delaying or missing pills are lacking.

Safety

Progestin-only methods are one of the safest options for contraception, with few contraindications to use; those listed include known or suspected pregnancy, known or suspected carcinoma of the breast or other progestin-sensitive cancer, undiagnosed abnormal uterine bleeding, hypersensitivity to any component of the product, benign or malignant liver tumors, and acute liver disease.²

The CDC Medical Eligibility Criteria for Contraceptive Use guidelines offer guidance for progestin-only pills, indicating a category 3 (theoretical or proven risks usually outweigh the advantages) or category 4 (unacceptable health risk, method not to be used) for only a select number of additional conditions. These conditions include a history of malabsorptive bariatric surgery (category 3) and concurrent use of medications that induce hepatic enzyme activity (category 3)—such as phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine, rifampin, and rifabutin.⁹ These conditions are included primarily due to concerns of decreased effectiveness of the contraception

and not necessarily because of evidence of harm with use.

The prevalence of consumers with contraindications to progestin-only pills appears to be low. In a large database study, only 4.36% seeking preventive care and 2.29% seeking both preventive and contraceptive services had a contraindication to progestin-only pills.¹⁰ Therefore, candidates for norgestrel use include individuals who have commonly encountered conditions, including those who⁹:

- have recently given birth
- are breastfeeding
- have a history of venous thromboembolism
- smoke
- have cardiovascular disease, hypertension, migraines with aura, or longstanding diabetes.

Adverse effects

The most common adverse effects (AEs) related to norgestrel use are bleeding changes.² In the initial clinical studies for FDA approval, about half of enrolled participants reported a change in bleeding; about 9% discontinued the contraceptive due to bleeding. Breakthrough bleeding and spotting were reported by 48.6% and 47.3% of participants, respectively. About 6.1% had amenorrhea in their first cycle; 28.7% of participants had amenorrhea overall. Other reported AEs were headache, dizziness, nausea, increased appetite, abdominal pain, cramps or bloating, breast tenderness, and acne.

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Progestin-only methods of contraception are one of the safest, with few contraindications, making those who have commonly encountered conditions candidates for use

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Fast facts about norgestrel^{1,2,12}

- **Brand name:** Opill
- **Class:** Progestin-only contraception
- **Indication:** Pregnancy prevention
- **Approval date:** Initial approval in 1973, nonprescription approval on July 13, 2023
- **Availability date:** 2024
- **Manufacturer:** Perrigo Company, HRA Pharma, Paris, France
- **Dosage forms:** 0.075 mg tablet

FDA approval required determining appropriate direct-to-patient classification

As part of the process for obtaining nonprescription approval, studies needed to determine that patients can safely and effectively use norgestrel without talking to a health care provider first. As part of that process, label comprehension, self-selection, and actual-use studies were required to demonstrate that consumers can use the package information to determine their eligibility and take the medication appropriately.

The ACCESS study

Research Q: *Do patients appropriately determine if the contraceptive is right for them?*

Study A: *Yes, 99% of the time.*

In the Adherence with Continuous-dose Oral Contraceptive: Evaluation of Self-Selection and Use (ACCESS) pivotal study, which evaluated prescription to nonprescription approval, participants were asked to review the label and determine whether the product was appropriate for them to use based on their health history.¹¹ Approximately 99% of participants (n = 1,234/1,246) were able to correctly self-select whether norgestrel was appropriate for their own use.¹²

Research Q: *After beginning the contraceptive, do patients adhere to correct use?*

Study A: *Yes, more than 90% of the*

time (and that remained true for subpopulations).

In the next phase of the ACCESS study, eligible participants from the self-selection population who purchased norgestrel and reported using the product at least once in their e-diary over a 6-month study period comprised the “User Population.”¹² The overall adherence to daily pill intake was 92.5% (95% confidence interval [CI], 92.3–92.6%) among the 883 participants who contributed more than 90,000 days of study participation, and adherence was similarly high in subpopulations of individuals with low health literacy (92.6%; 95% CI, 92.1–93.0), adolescents aged 12–14 years (91.8%; 95% CI, 91.0–92.5%), and adolescents aged 15–17 years (91.9%; 95% CI, 91.4%–92.3%).

Research Q: *When a pill was missed, did patients use backup contraception?*

Study A: *Yes, 97% of the time.*

When including whether participants followed label instructions for mitigating behaviors when the pill was missed (eg, take a pill as soon as they remember, use backup contraception for 2 days after restarting the pill), adherence was 97.1% (95% CI, 97.0–97.2%). Most participants missed a single day of taking pills, and the most common reported reason for missing pills was issues with resupply as participants needed to get new packs from their enrolled research site, which should be less of a barrier when these pills are available over the counter.

Clinical implications of expanded access

Opportunities to expand access to effective contraception have become more critical in the increasingly restrictive environment for abortion care in the post-*Dobbs* era, and the availability of norgestrel to patients without prescription can advance contraceptive equity. Patients encounter many barriers to accessing prescription contraception, such as lack of insurance; difficulty with scheduling an appointment or getting to a clinic; not having a regular clinician or clinic; or

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As part of the FDA approval process, studies needed to verify patients’ label comprehension and self-selection and evaluate their actual use

FIGURE Patient information sheet on Opill (norgestrel 0.075 mg) oral contraceptive pill

What is the Opill?	<ul style="list-style-type: none"> Opill is a daily birth control pill that contains norgestrel, which is a progestin. This type of contraception is often called a progestin-only pill, or POP, because it does not contain any estrogen. Opill is the first hormonal birth control pill that has been approved for purchase over the counter without a prescription. This pill is not used for emergency contraception (sometimes known as the morning after pill).
How does it work?	<ul style="list-style-type: none"> This birth control pill works to prevent pregnancy by causing cervical mucus to become thick, which blocks sperm from traveling into the uterus. In about half of users it can also prevent ovulation, or the release of an egg from the ovary.
Who should not use this pill?	<p>People should not use this pill if:</p> <ul style="list-style-type: none"> They may be pregnant They have a history of or current breast cancer or other progestin-sensitive cancer They have abnormal vaginal bleeding that has not been evaluated yet They have an allergy to any component of the pill They have liver tumors or acute liver disease
What are the side effects?	<ul style="list-style-type: none"> The most common side effect is changes in menstrual bleeding. Other side effects include headache, dizziness, nausea, increased appetite, abdominal pain, cramps or bloating, breast tenderness, and acne.
How do you use it?	<ul style="list-style-type: none"> The pill can be started on any day of the cycle. Use a nonhormonal back-up method, like condoms, for the first 2 days after starting the pills. Take the pill at the same time each day. If you miss a pill, take a pill as soon as you remember and continue taking the pills at your usual time. That means you could be taking 2 pills in one day. If you miss a pill, use a nonhormonal back-up method, like condoms, for the next 2 days until the pills start working on their own again.
When should you contact a health care provider?	<p>You should contact a health care provider if you have any questions or concerns about starting or using the pills. Examples of when to contact a health care provider include:</p> <ul style="list-style-type: none"> If you think you may be pregnant If you are not sure if the pill interacts with medications you are taking If you recently took emergency contraception If you have symptoms of new migraines or jaundice (yellowing of the eyes or skin) when taking the pill

health care providers requiring a visit, exam, or test prior to prescribing contraception.^{13,14} For patients who face these challenges, an alternative option is to use a nonprescription contraceptive, such as barrier or fertility awareness-based methods, which are typically associated with higher failure rates. With the introduction of norgestrel as a nonprescription contraceptive product, people can have direct access to a more effective contraceptive option.

A follow-up study of participants who had participated in the ACCESS actual-use study demonstrated that most (83%) would be likely to use the nonprescription method if available in the future for many reasons, including convenience, ease of access, ability

to save time and money, not needing to visit a clinic, and flexibility of accessing the pills while traveling or having someone else get their pills for them.¹⁴ Furthermore, a nonprescription method could be beneficial for people who have concerns about privacy, such as adolescents or individuals affected by contraception sabotage (an act that can intentionally limit or prohibit a person's contraception access or use, ie, damaging condoms or hiding a person's contraception method). This expansion of access can ultimately lead to a decrease in unintended pregnancies. In a model using the ACCESS actual-use data, about 1,500 to 34,000 unintended pregnancies would be prevented per year based on varying model

parameters, with all scenarios demonstrating a benefit to nonprescription access to norgestrel.¹⁵

After norgestrel is available, where will patients be able to seek more information?

Patients who have questions or concerns about starting or taking norgestrel should talk to their clinician or a pharmacist for additional information (FIGURE 2). Examples of situations when additional clinical evaluation or counseling are recommended include:

- when a person is taking any medications with possible drug-drug interactions
- if a person is starting norgestrel after taking an emergency contraceptive in the last 5 days
- if there is a concern about pregnancy

- when there are any questions about adverse effects while taking norgestrel.

Bottom line

The nonprescription approval of norgestrel, a progestin-only pill, has the potential to greatly expand patient access to a safe and effective contraceptive method and advance contraceptive equity. The availability of informational materials for consumers about potential issues that may arise (for instance, changes in bleeding) will be important for initiation and continuation of this method. As this product is not yet available for purchase, several unknown factors remain, such as the cost and ease of accessibility in stores or online, that will ultimately determine its public health impact on unintended pregnancies. ●

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As the norgestrel 0.075 mg contraceptive product is not yet available for purchase, several unknown factors remain, such as cost and ease of accessibility in stores or online, that will ultimately determine its public health impact on unintended pregnancies

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