

This memorandum reflects my conclusions regarding new drug application (NDA) 017031, supplement 41 for full prescription-to-nonprescription switch of norgestrel tablets 0.075 mg. This memorandum corrects an earlier version of this memorandum, dated July 10, 2023, by adding finalization dates for certain reviews cited in Section III. The recommendations and conclusions in this memorandum have not changed.

Decisional Memorandum

New Drug Application 17031 Supplement 41

Application for Full Prescription-to-Nonprescription Switch of Norgestrel Tablets 0.075 mg

Proposed Use: "To prevent pregnancy"

Karen Minerve Murry, MD, FACE
Deputy Director, Office of Nonprescription Drugs
United States Food and Drug Administration

- I. Summary of Decision
- II. Background
- III. Materials Reviewed
- IV. Scientific Challenges of the Application
- V. Likely Efficacy in the Nonprescription Setting
- VI. Safety Issues in the Nonprescription Setting
- VII. Labeling Issues

I. Summary of Decision

Approval of norgestrel 0.075 mg oral tablet (hereafter referred to as norgestrel tablet) for nonprescription daily contraception is appropriate. The potential benefits of an increase in the ability for consumers to prevent unintended pregnancy (with its attendant medical, economic, and societal harms) outweigh the potential risks of the product in the nonprescription setting. While the data submitted by the applicant in support of the appropriateness of nonprescription status for norgestrel tablets had some limitations, the sum of the data from the applicant's program and other sources was supportive. Dr. Christine Nguyen, Deputy Director of the Office of Rare Diseases, Pediatrics, Urology, and Reproductive Medicine concurs with the decision for approval, and has signed a joint review to that effect (primary author Dr. Anandi Kotak).

II. Background

I refer the reader to the excellent reviews by FDA staff of multiple scientific disciplines who carefully reviewed this application. Their reviews contain the detailed results, reasoning, and literature references upon which I base my decision. In particular, the Division Director Summary Review by Dr. Pamela Horn of the Division of Nonprescription Drugs II provides a thoughtful and well-crafted overall summary and rationale supporting approval. This memorandum summarizes a few key findings of the various reviews.

In this memorandum, when referring to people who can become pregnant, I have sometimes used the word person or people, and sometimes woman or women. I note that not every person who can become pregnant identifies as a woman.

Norgestrel 0.075 mg tablet was originally approved as a daily oral contraceptive in 1973. Norgestrel is a progestin; this product does not contain an estrogen. The product was marketed under the brand name Ovrette until 2005, when distribution was stopped by the company for marketing reasons, and not for

reasons of safety or effectiveness. Beginning in 2015, HRA Pharma (now owned by Perrigo) met with FDA multiple times to obtain advice on a nonprescription development program. On June 14th, 2022, HRA submitted a supplemental application for a full prescription-to-nonprescription switch of the product. On October 13th, 2022, HRA submitted a major amendment to the supplemental application. On May 9th and 10th, 2023, a public Advisory Committee meeting was held, at which certain challenging issues of the application were discussed.

Although effective forms of prescription contraception exist, people can face challenges in obtaining them. Multiple reasons exist, including the need to take off work (often losing income) or school; lack of health insurance; lack of an established relationship with a healthcare provider; healthcare provider shortages in many areas; stigma; difficulty obtaining transportation; and others. Half of all pregnancies (3 million of 6 million pregnancies per year) in the US are unintended, pointing to a need for increased availability of effective contraception for people who are not intending to become pregnant. Among adolescents, the rate of unintended pregnancy is particularly high; among 15-17-year-olds, 72% of all pregnancies are unintended (Finer 2016). The rate of unintended pregnancy is five times higher among women who live in poverty than among high-income women (Finer 2011). Unintended pregnancy has many potential negative consequences- for the person who experiences the unintended pregnancy, for children, for US society, and for the public health. As noted in the clinical reviews by Dr. Kotak and others, some of these potentially negative consequences include:

- Lack of preconception care, with lack of management of medical conditions that increase risk for mother and fetus
- Lack of early recognition of pregnancy, with late or no initiation of prenatal care, and attendant increased risk of poor maternal and fetal outcomes
- Increased risk of preterm birth and low birth weight
- Increased risk of maternal depression
- Increased risk of maternal substance use
- Poor maternal-infant bonding
- Decreased rates of breastfeeding, with loss of the positive benefits to the infant associated with breastfeeding
- Increased rates of child neglect and abuse
- Increased risk of infant death in the first year of life
- Increased relationship stress between mother and partner

Direct medical costs for unintended pregnancy in the US have been estimated at over \$5 billion per year (Trussell 2007). Multiple other costs exist, such as lost wages during pregnancy and care of the child, decreased earnings related to decreased/delayed educational attainment, and direct costs of care of the child.

In addition to the above, even an intended pregnancy is not without some maternal risk, thus underscoring the need for people to be able to maximize planning of their pregnancies, and not become pregnant until they are medically, emotionally, and economically ready to go through pregnancy and raise a child.

Prevention of pregnancy has become even more important in recent times, as increasingly, women in some parts of the US have few options once an unintended pregnancy occurs. Thus, giving women

greater ability to prevent a pregnancy, rather than to face wrenching personal choices after an unintended pregnancy occurs, has the potential for individual and societal benefit.

III. Materials Reviewed

Division Director review by Dr. Pamela Horn of the Division of Nonprescription Drugs II (DNP2) (DARRTS 2023 06 12)

Clinical review by Dr. Jeena Jacob of DNP2 (DARRTS 2023 06 06)

Joint Clinical review by Drs. Anandi Kotak and Audrey Gassman of the Division of Urology, Obstetrics, and Gynecology (DUOG); and by Dr. Christine Nguyen of the Office of Rare Diseases, Pediatrics, Urology, and Reproductive Medicine (ORDPURM) (DARRTS 2023 06 12)

Joint Social Science (Ms. Barbara Cohen) and Biostatistics (Dr. Rongmei Zhang) reviews of the pivotal Drug Facts Label Comprehension Study, Targeted Breast Cancer Self-Selection Study, Pivotal Actual Use Trial Self-Selection Phase, and Consumer Information Leaflet Comprehension Study (DARRTS 2023 06 05)

Biostatistics review by Dr. Rongmei Zhang of the pivotal Actual Use Trial (DARRTS 2023 06 07)

Decision Support Memorandum by Dr. Leila Lackey of the Decision Support and Analysis Staff in the Office of Planning and Strategic Analysis (DARRTS 2023 06 14)

Interdisciplinary Science labeling review by Dr. Hana Mujahid (DARRTS 2023 06 05)

Labeling review by Dr. Grace Jones of the Division of Medication Error Prevention and Analysis (DARRTS 2023 06 08)

Office of Scientific Investigations clinical inspection summary by Dr. John Lee (DARRTS 2023 02 28)

Consultation on potential for bone effects, by Dr. Olivia Easley of the Division of General Endocrinology (DARRTS 2023 02 08)

Consultation on adolescent use, by Dr. Amy Taylor of the Division of Pediatric and Maternal Health (DARRTS 2022 08 22)

Nonclinical memorandum by Dr. D. Charles Thompson of the Pharmacology/Toxicology Staff of the Office of Nonprescription Drugs (DARRTS 2022 09 16)

Chemistry, Manufacturing, and Controls review by Dr. Sreenivasa Eturi (Panorama 2023 06 19)

Environmental Assessment review by Dr. Xiaoqin Wu (Panorama 2023 06 16)

Clinical Pharmacology memorandum by Dr. Li Li (DARRTS 2023 06 14)

Applicant's initial supplemental application (2022 06 14) and subsequent supporting submissions (58 additional submissions as of 2023 06 20)

IV. Scientific Challenges of the Application

In order to demonstrate that prescription status is not needed for a drug, the applicant must provide consumer behavior data to demonstrate that people are likely to use the drug safely and effectively

without the intervention of a healthcare provider. In this application, most of that scientific support was provided by labeling comprehension studies and self-selection studies, which in general demonstrated very good consumer comprehension of almost all important labeling messages, although the percentage of participants with limited literacy was not as high as FDA requested. The applicant also conducted an Actual Use study, ACCESS (Adherence with Continuous-Dose Oral Contraceptive: Evaluation of Self-Selection and Use), which unfortunately had a significant problem (described below) that limited its usefulness in assessing likely consumer behavior in certain circumstances, particularly around taking the medication every day, and at the same time of day. Consistent daily use and consistent timing of dosing are considered important for optimal effectiveness of norgestrel tablet contraception, and may reduce the occurrence of breakthrough vaginal bleeding.

The “Improbable Dosing” Observations

During review of the ACCESS Use Phase, FDA noted that 30% of participants reported a total number of tablets taken that exceeded the total number of tablets dispensed. FDA requested that the applicant conduct a comprehensive root cause analysis to determine the cause of this observation; no clear cause was determined. An inspection by the FDA’s Office of Scientific Integrity did not identify a definitive root cause of the over-reporting, but also did not identify violations of Good Clinical Practice. Even among participants who did not report a total number of tablets taken that exceeded the total number of tablets dispensed, a large percentage (39%) reported taking more than one tablet on at least one day of study, with some reporting taking up to five tablets in a single day. It seems likely that this was a phenomenon of pervasive over-reporting, rather than of actually taking multiple doses per day, but this is not known with certainty.

This problem was likely related to design flaws in the eDiary; excessive and confusing prompting; financial incentives for over-reporting; or a combination of these issues. Please see Section 8.3.1 of Dr. Jacob’s review for a thorough description of the over-reporting and its potential causes. Among analyses conducted by FDA were “worst-case scenario” analyses which counted as incorrect all responses of participants who had reported taking more tablets than they were dispensed. The pervasive over-reporting of dosing makes it very difficult to assess the primary outcomes of ACCESS, which were intended to answer the question of whether consumers are likely to take norgestrel tablet every day, and at approximately the same time every day. If we assume that worst-case scenario analyses reflect the true likelihood of correct daily use, nonprescription availability of norgestrel tablet might only result in a modest improvement in nonprescription contraceptive overall effectiveness (and only a modest reduction in unintended pregnancies) in the US, compared to the status quo. However, if people who reported taking multiple tablets on multiple days actually took one tablet on each of those days, and that use pattern reflects use in a real-world setting, norgestrel tablet would likely provide a substantially more effective option for nonprescription contraception.

Some reassuring information comes from the other consumer behavior studies done for the program. For example, in the pivotal label comprehension study, >90% of participants understood messages about taking norgestrel tablet daily, and at the same time each day.

The most difficult part of the decision-making process for this application was related to whether to approve despite the uncertainty due to the improbable results seen for at least 30% of participants in the ACCESS Actual Use phase. The decision is made based on the totality of evidence and on the benefit:risk calculus that includes a favorable risk:benefit equation for individual consumers, and the

possibility of at least a moderate, and perhaps a large, reduction in unintended pregnancies, with the potential for attendant public health benefits. FDA and Industry have both learned from the problems seen in ACCESS, and FDA will expect future sponsors to include design elements that will decrease the likelihood of inaccurate reporting in Actual Use studies (while maintaining a naturalistic use setting), and to conduct preliminary studies that demonstrate correct eDiary reporting prior to conduct of a pivotal Actual Use study. While ACCESS did not provide reliable data regarding likelihood of consistent daily use, it did provide some information on pregnancy incidence, and some safety information.

Advisory Committee Discussion

At the May 9-10, 2023, public Advisory Committee meeting, advisors voted unanimously that, in their opinion, the potential benefits of nonprescription norgestrel 0.075 mg daily tablet contraception availability outweighed the potential risks. They expressed a strong belief that there is a major unmet public health need for increased access to effective contraception; that consumers are likely to take norgestrel tablet daily; and that norgestrel tablet is very safe. When explaining their votes, committee members generally stated that they had based their vote on personal clinical or prior scientific experience, and their perception of the potential for a public health benefit, and did not express significant concern over the data challenges and findings of the consumer behavior studies submitted in support of the application.

V. Likely Efficacy in the Nonprescription Setting

At the time of the 1973 prescription approval for norgestrel 0.075 mg tablets, FDA determined that the product was effective as a daily oral contraceptive in preventing pregnancy, with a Pearl Index of 2.3 pregnancies per 100 person-years of exposure. The pivotal Actual Use trial conducted for the nonprescription development program was titled ACCESS (for Adherence with Continuous-Dose Oral Contraceptive: Evaluation of Self-Selection and Use). ACCESS was not powered to obtain a precise Pearl Index. However, a reasonable estimate from that trial is a Pearl Index of 4.4 (95% CI 1.9-8.8), obtained by excluding subjects who had improbable dosing reported in their eDiaries. Per Dr. Kotak's review, real-world evidence from the published literature indicates that the Pearl Index in real-world use after a nonprescription approval will likely be higher, perhaps in the range of 7% or somewhat higher.

When comparing the likely Pearl Index of norgestrel 0.075 mg tablets in the nonprescription setting to the Pearl Index of currently available nonprescription contraceptive methods, norgestrel 0.075 mg compares favorably. Currently available nonprescription contraceptive methods include male and female condoms, and spermicides. These available methods have Pearl Indices between 14-28%. Thus, if people who are currently using either another form of nonprescription birth control (or no birth control at all) switch to using nonprescription norgestrel, they will be substantially less likely to experience unintended pregnancy. An analysis by our Decision Support colleagues looked at the types of contraception used at baseline in ACCESS; among these were 35% of participants who used no contraception at all at entry, which would be expected to have a 12-month contraceptive failure rate of 85%. Looking at all methods of contraception (including some that are known to be more effective than norgestrel 0.075 mg daily tablets) used at baseline in ACCESS, the overall weighted average of the expected 12-month contraceptive failure rate was estimated at 38-41%. It is extremely likely that norgestrel tablet contraception will have a lower 12-month failure rate than 38%, and thus efficacy (meaning a reduction in unintended pregnancy compared to the status quo) in the nonprescription setting is very likely.

It is conversely possible that some people who are currently using a prescription form of contraception will switch to using nonprescription norgestrel tablets. As noted earlier, there are currently considerable barriers to obtaining prescription contraception, and thus people might switch. When used correctly, some prescription forms of birth control (especially intrauterine devices and implants) are more effective than nonprescription daily norgestrel tablets would likely be. Thus, in a hypothetical group of people who switch from highly effective prescription contraception to nonprescription norgestrel tablets, marginally more unintended pregnancies might occur than would have occurred if the users had continued to go through the process of obtaining prescription contraception. The Consumer Information Leaflet for nonprescription norgestrel tablets contains a table showing the relative effectiveness of different forms of contraception, and thus information regarding this issue will be available to consumers.

Overall, I expect that the availability of nonprescription norgestrel tablet will result in a substantial increase in use of effective contraception among people who wish to avoid unintended pregnancy. I expect this to be particularly true among people who currently experience significant barriers to obtaining contraception, for example people who live in poverty, those who cannot take off from work or school to attend physician appointments, and adolescents. Nonprescription norgestrel tablet contraceptive availability has the potential to reduce the number of unintended pregnancies in the United States, and thereby to reduce the many negative medical and socioeconomic impacts of unintended pregnancy.

Also of substantial benefit could be an increase in bodily autonomy that this product could provide to women. Use of norgestrel tablet will not depend on a partner agreeing, in the moment, to interrupt intercourse or use a male condom. A woman could plan ahead, use norgestrel tablets properly, and know that she is unlikely to become pregnant. Use of condoms will continue to be important for protection against sexually transmitted diseases; responsible people will presumably continue to use them to protect themselves and their sexual partners. There is some risk that some people who currently use condoms primarily to avoid causing pregnancy, and not specifically for prevention of sexually transmitted disease, will be less likely to use a condom if the female partner is known to be using norgestrel tablets for contraception. The Drug Facts label for nonprescription norgestrel tablets contains a warning that norgestrel tablets do not protect against sexually transmitted diseases, and the Consumer Information Leaflet informs the consumer that only condoms protect from sexually transmitted diseases.

With regard to their reproductive health today, US women and others with the potential to become pregnant face many challenges. Nonprescription availability of this daily oral progestin-only contraceptive has the potential to at least marginally, and perhaps substantially, lower some of the barriers to reproductive self-care and bodily autonomy for American people.

VI. Safety Issues in the Nonprescription Setting

Overall, adverse events in the nonprescription norgestrel 0.075 mg tablet development program were qualitatively and quantitatively similar to those seen in the prescription development program and postmarketing experience.

Among the risk concerns for norgestrel tablets, the following are of most concern to the review team:

- Use of the product by people with progestin-sensitive cancers, with the risk for worsening the clinical course of the cancer, or increasing risk of recurrence
- The high frequency of vaginal bleeding with the product, with the risk that people using the product will attribute vaginal bleeding to the product and not recognize the need to seek evaluation for serious conditions that manifest with vaginal bleeding
- The potential for reduction in bone mineral density, and perhaps increased fracture risk, with very long-term use of the product

While there is biological plausibility for an increase in risk of cancer progression or recurrence associated with use of a progestin by someone with a progestin-sensitive cancer, the precise degree of increase in risk is not known. In the targeted Self-Selection study conducted in 206 people with current or past breast cancer, 95% (95% CI 91-97) correctly deselected for use of norgestrel tablet. When examining the incorrect selectors, most reported seeing their physician at least twice per year, which provides an additional safeguard. It should be noted, as Ms. Cohen points out, that even under the care of a healthcare professional, women with breast cancer are sometimes prescribed hormonal contraception—this was true of 11 women at baseline in the targeted breast cancer self-selection study. In the self-selection phase of ACCESS, three people with a history of progestin-sensitive cancers did not correctly deselect; they were not permitted to purchase the study drug or proceed into the Actual Use phase. Progestin-sensitive cancers are uncommon in people under age 40 years, and the population using norgestrel tablet for contraception would likely overwhelmingly be under the age of 40 years. Nevertheless, it seems likely that a small percentage of women of reproductive potential who fall into that small group with current or prior progestin-sensitive cancers will incorrectly purchase and use this product, and it is biologically plausible that a small percentage of those incorrect users will experience worsening or recurrence of their cancer. For an individual consumer of the product, the risk is very low, and almost nonexistent if they read and follow the labeling. Overall, the total public health impact of the potential harm related to incorrect use by people with progestin-sensitive cancer is likely outweighed by the probable larger public health impact of prevention of a large number of unintended pregnancies with all their attendant harms.

Norgestrel tablets are taken daily, with no break in use, and thus people taking it are not expected to have a regular monthly menstrual period. Unexpected vaginal bleeding is the most common adverse event associated with prescription use of norgestrel tablets, and occurred in 21% of participants in ACCESS. It is more likely to be a tolerability issue rather than a safety issue. That is, the unexpected bleeding is unlikely to have serious medical consequences, but the inconvenience and unpleasantness of unpredictable bleeding may lead some consumers to discontinue use. In the age group most likely to use norgestrel tablet contraception, serious conditions associated with abnormal uterine bleeding are uncommon. Per Dr. Jacob's review and SEER 2019 data, endometrial cancer is rare in women of reproductive age, occurring in only 0.037% of women under age 50 years.

While depot medroxyprogesterone acetate (DMPA) is associated with decreased bone mineral density, its effects are probably not comparable to those of norgestrel 0.075 mg daily, because DMPA strongly suppresses estrogen, while norgestrel 0.075 mg/day does not. In the literature, norgestrel itself has not been associated with decreased bone mineral density or increased fracture risk. The prescription labeling for progestin-only oral contraceptives does not recommend monitoring of bone mineral density. While the long-term effect on bone density and risk of fracture is not completely characterized

for norgestrel 0.075 mg daily, the preservation of some degree of estrogen secretion would be expected to be somewhat protective.

In ACCESS, there was one reported case of mural thrombus of the internal jugular vein. The person with the event had comorbidities of atherosclerosis and hypertension, and a family history of “premature” atherosclerosis. Venous thromboembolism (VTE) is an adverse event more typically associated with estrogen-containing contraceptives, rather than with progestin-only contraceptives (although VTE has been reported with DMPA). The significance of the occurrence of this single event of VTE in ACCESS is uncertain. No VTEs occurred in the prescription development program for norgestrel tablets. Of note is the fact that the risk of VTE with pregnancy is higher than the risk of VTE even with estrogen-containing contraceptives.

As noted earlier, norgestrel is a progestin, and this product does not contain an estrogen. Many of the safety concerns associated with daily oral contraceptives in general are related to the estrogen content of combined progestin/estrogen tablets. Combined oral contraceptives have a higher risk of thromboembolic and other cardiovascular events, particularly among people who smoke and are over age 35 years. Hypertension is also more of a concern for combined oral contraceptives than for progestin-only daily tablets. Thus, when considering a candidate for the first nonprescription daily oral tablet, norgestrel, being progestin-only, has fewer known safety concerns than a combined oral contraceptive would.

Regarding use in adolescents, I agree with the clinical team and the Division of Pediatric and Maternal Health that the benefits and risks are similar between adolescents and adults, and that nonprescription norgestrel tablets should be available for adolescents as well as adults.

To summarize the likely risks associated with nonprescription norgestrel tablet use, they are qualitatively and quantitatively similar to the risks seen with prescription norgestrel tablet use. It is possible that widespread use of norgestrel tablet contraception in the nonprescription setting will have some unintended harms, e.g., worsening or recurrence of progestin-sensitive cancers; sexually transmitted diseases if condom use declines; or delay in evaluation of conditions that manifest as vaginal bleeding. However, these conditions are all addressed in the labeling of the product, and the benefit:risk ratio for the individual consumer is favorable. Also, the overall negative public health impact of these adverse outcomes is expected to be less than the positive public health impact of prevention of unintended pregnancies.

VII. Labeling Issues

As of the time of writing of this memorandum, labeling negotiations are ongoing with the applicant, and therefore final labeling may differ from what is discussed below.

In the pivotal Label Comprehension Study for the Drug Facts label, the applicant met prespecified thresholds for comprehension for most endpoints, but comprehension of two statements of note did not meet thresholds:

“If you are more than 3 hours late taking your tablet or miss taking your tablet, use a condom or other barrier method every time you have sex during the next 2 days” (83% comprehension, 95% CI 80-87)

Because of this, Ms. Cohen and Dr. Zhang recommended addition of a message to the blister pack advising the use of back-up contraception for 48 hours after a missed dose. The blister pack is seen every time a consumer takes a tablet, and viewing the blister pack's pattern of used tablets is a likely way that consumers will realize they have missed a dose. Therefore, the blister pack is a logical place to have a message about what to do when a dose is missed.

"Do not use as an emergency contraceptive (morning after pill). This product does not prevent pregnancy when used after unprotected sex." (76% comprehension, 95% CI 71-79)

Because of this, Ms. Cohen and Dr. Zhang recommended addition of a statement to the product's Principal Display Panel (PDP) reminding consumers that this product is not an emergency contraceptive. The Principal Display Panel is the outer carton panel most likely to be first viewed by a consumer considering purchase of norgestrel tablets. When consumers are trying to decide between purchasing a routine daily oral contraceptive, or an emergency contraceptive, it may be helpful to have an explicit statement on the norgestrel tablet PDP informing consumers that this product is not an emergency contraceptive.

The applicant agreed to the above labeling changes.

VIII. References

Please refer to the above FDA reviews for literature references for most material in this memorandum. Additional references follow for statements not specifically included in those reviews, but cited in this memorandum:

Finer L and Zolna M 2011. Unintended pregnancy in the United States: incidence and disparities. *Contraception* 84: 478-85

Finer L and Zolna M 2016. Declines in unintended pregnancy in the United States, 2008-2011. *N Engl J Med.* 374(9):843-52.

Trussell J 2007. The cost of unintended pregnancy in the United States. *Contraception* 75: 168-170

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

/s/

KAREN M MURRY
07/13/2023 07:30:13 AM