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First OTC Oral Contraceptive Has Advisory Panel's Unanimous Support Despite FDA's Data Concerns

by Malcolm Spicer

FDA officials again made clear concerns about "improbable dosing" data in HRA's sNDA for 0.075-mg norgestrel tablet branded Opill before advisory panel voted at close of a two-day meeting conducted 60 years after first Rx oral contraceptive approved in US.

Some members of a Food and Drug Administration advisory panel had questions and others didn't about HRA Pharma's actual user study data but all voted to recommend the agency approve the firm's proposal for the first OTC switch of an oral contraceptive in the US.

FDA officials again made clear their concerns about "improbable dosing" data in HRA's supplement new drug application for its 0.075-mg norgestrel tablet branded Opill before the panel voted on 10 May at the close of a two-day meeting conducted online 60 years after the first Rx oral contraceptive was approved in the US.

The agency has about three months to let HRA as well as consumers know whether its doubts will impede approving the *Perrigo Company PLC* subsidiary's proposal.

"Today's vote reflects the strong data showing that
Opill can be used safely and effectively over-the-counter," said Frederique Welgryn, Perrigo's women's health vice president.

The advisory panel's recommendation is non-binding. While the FDA's decisions track with the recommendations more often than not, one of its notable diversions from its advisors' thinking was in its rejection of the initial proposal for OTC sales of the Plan B (levonorgestrel / 2 x 0.75-mg) emergency contraceptive in 2013.

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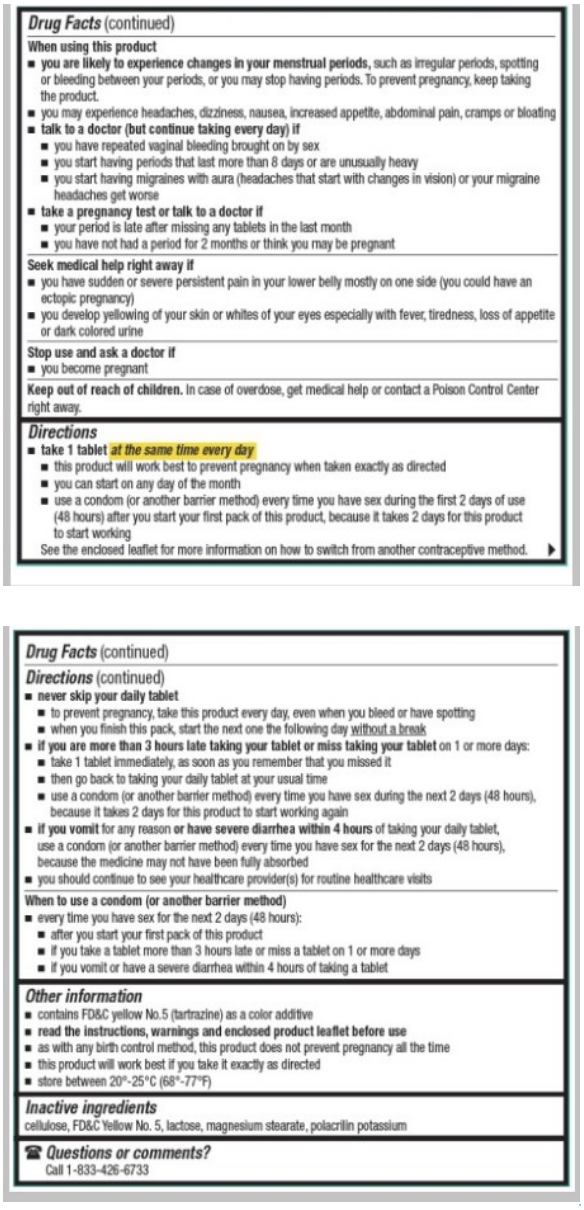
A leading advocate in the Senate for expanding access to



Drug Facts (continued)

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

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

Stop use and ask a doctor if
- you become pregnant

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

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

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

Drug Facts (continued)

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

When to use a condom (or another barrier method)
- every time you have sex for the next 2 days (48 hours):
  - after you start your first pack of this product
  - if you take a tablet more than 3 hours late or miss a tablet on 1 or more days
  - if you vomit or have 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

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)
- 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

HRA'S APPLICATION FOR OPILL INCUDED A DFL PRINTED ACROSS THREE PANELS, ABOVE AND BELOW, AND GENERATED PLENTY OF DISCUSSION DURING AN FDA ADVISORY PANEL MEETING BEFORE THE MEMBERS VOTED UNANIMOUSLY TO RECOMMEND APPROVAL.

Source: Source: HRA

contraception and for other women's health issues, Washington Democrat Patty Murray, alluded to the FDA's decision on Plan B in a statement.

"FDA should trust the experts – who voted unanimously in support of this application – and must not delay in getting over-the-counter birth control on the shelves for American women," Murray said.

When HRA submitted its sNDA in July 2022, the deadline under the prescription drug user fee program for the FDA to make a decision on the application was 11 May. Perrigo said the date would be extended 90 days due when the FDA in October, after asking HRA to explain the

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improbable dosing data, postponed the advisory panel meeting originally scheduled for November. (Also see "*US FDA Requests More Information, Needs More Time To Review Birth Control OTC Switch Proposal*" - HBW Insight, 26 Oct, 2022.)

The progestin-only product was approved for Rx sales in the US in 1973 and remained available through 2005 when HRA discontinued sales as combination ingredient oral contraceptives claimed dominant market share.

'Realize How Important It Is'

FDA officials speaking during the meeting of the Nonprescription Drug and Obstetrics, Reproductive and Urologic Drugs advisory committees didn't state doubts about the safety and efficacy of 0.075-mg norgestrel tablets available Rx in the US or about the public health benefit from expanding access to oral contraceptives.

Agency officials were clear, however, about their doubts about some of HRA's OTC actual use trial data. (Also see "*Cloud Over FDA Advisory Panel Meeting From 'Over-Reporting' In Birth Control OTC Switch Study*" - HBW Insight, 10 May, 2023.)

"I just want to emphasize from the FDA that we really realize how important it is that women have increased access to effective contraception. And I don't want I don't want any of our discussion or our pointing out the deficiencies of the development program to take away from that message," said Karen Murray, deputy director of the Center for Drug Research and Evaluation's Office of Nonprescription Drugs.

Speaking before the committees prepared to discuss their recommendation and other questions the FDA presented about OTC oral contraceptives, Murray explained why the agency asked the panel to consider whether "improbable dosing" data could make the overall actual use study results unreliable.

The questioned data indicated some participants, using the electronic diaries provided in the study, reported taking Opill on more days than they did or taking a tablet when they didn't have any. The over-reporting wasn't identified by HRA but by FDA staff reviewing the firm's SNDA.

"When a development program is proposed for a nonprescription drug, we can't just approve it based on the experience in the prescription setting without the applicant doing adequate studies to look at what's likely to happen in the nonprescription setting," Murray said.

Year After Acquisition, Perrigo Waits For US Decision On HRA's OTC Oral Contraceptive Switch

By Malcolm Spicer

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"It would have been a much easier time for the agency if the applicant had submitted a development program and an actual use study that was very easy to interpret and did not have so many challenges. But that was not what happened for us. So the FDA has been put in a very difficult position of trying to determine whether it is likely that women will use this product safely and effectively in a nonprescription setting."

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Wait will be as long as another three months to learn whether HRA will have approval to market OTC a product Perrigo estimates will have $100m in annual sales.

Read the full article here

Members: Let's Move To Recommending

The range of panel members' thinking about the over-reporting was evident in comments by Kathryn Curtis, an epidemiologist at the Centers for Disease Control and Prevention Division of Reproductive Health/Women's Health and Fertility Branch, and Katalin Roth, a professor of medicine at the George Washington University Hospital Division of Geriatrics and Palliative Medicine and an NDAC member.

They made their comments during the committees' response the FDA's request for recommendations for changes to HRA's actual use study design if it asked the firm to conduct another study (see related story).

"The improbable dosing issue is important and I don't think it's been adequately addressed and certainly leads to some uncertainty in the findings. But despite this, I would not recommend another actual use study at this time and I think we can make a decision on the totality of the evidence," said Curtis, participating as an ORUDAC member.

Roth, an NDAC member, expressed a different regard for over-reporting. "We're talking about birth control pills, which come in a package labeled day one through day 28," she said.

"The statistical problem that we're talking about is not about reporting adverse effects. It's not about reporting unintended pregnancies. It's only about whether the women in the study accurately reported or over-reported whether or not they took the pills," she added.

Over-Reporting In Previous OTC Switch Application

HRA/Perrigo's lead women's health executive speaking to the committees, scientific affairs senior director Irene Laurora, noted in response to a panel member's question that FDA officials had acknowledged participants' over-reporting wasn't caused by "systematic problems in the study."

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Laurora and other HRA staff and consultants working with the firm repeated at multiple points during their presentations that the over-reporting, which the FDA says it found from 30% of the participants, didn't affect the overall results of the actual use study.

"Our primary analysis showed you that people do understand how to take one pill a day and that they follow the label directions," Laurora said.

One of HRA's consultants, Arthur Stone, director of the Center for Self-Report Science and a professor of psychology, economics and public policy at the University of Southern California, pointed out that participants' over-reporting of their product also was found in an actual use trial conducted for another first-in-class OTC switch, overactive bladder drug Oxytrol for Women.

The FDA approved the 3.9-mg oxybutynin transdermal system in 2013 after an NDAC panel voted 6-5 to say the application sponsor had not shown consumers could safely self-select Oxytrol in an OTC setting. (Also see "*Oxytrol For Women Gets OTC Green Light As Rare First-In-Class Switch*" - HBW Insight, 28 Jan, 2013.)

Stone said over-reporting in the Opill actual use study reached the extent the FDA found "because the very rare conditions to allow for over-reporting of this kind existed."

The conditions were that HRA's study design allowed participants to continue to use their e-diaries when no pills were available to them.

"That's an extraordinary circumstance when that happens. It's happened a few times in the past. The Oxytrol trial was one example of that. When the conditions are right, people do this kind of over-reporting, but it is rare and it's rare because the conditions do not exist for it to be seen very often," Stone added

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