



FDA Change of Plan B One-Step Label Points to Consider

On December 23, 2022, the US Food and Drug Administration (FDA) changed its Drug Facts Label for Plan B One-Step (PBOS), removing language that, since 2006, had stated that PBOS “may inhibit implantation (by altering the endometrium).” The FDA’s action has created the impression that PBOS and similar, generic levonorgestrel-based drugs used for “emergency contraception” (LNG-EC) have no effect on the survival of a human being conceived following sexual assault.

Unfortunately, the FDA did not address all factors relevant to how LNG-EC can impact human life after fertilization. Specifically, the FDA did not fully address a well-known concern that LNG-EC can prevent pregnancy even after it fails to prevent ovulation. Since this important issue was not resolved and concerns about LNG-EC’s post-fertilization effects remain, The National Catholic Bioethics Center will maintain its longstanding position that Catholic health care institutions and professionals should ensure with moral certitude (that is, by excluding any reasonable doubts), at a minimum, that LNG-EC is not dispensed when it could not prevent ovulation but may well cause the death of an embryo. Catholics should resist legislation that requires dispensing of LNG-EC on the basis of a negative pregnancy test alone.

Review of the FDA’s Action and Arguments

What Did the FDA Do on December 23, 2022?

On December 23, 2022—the Friday before Christmas—the FDA changed its Drug Facts Label for Plan B One-Step (PBOS), removing language that, since 2006, had stated that PBOS “may inhibit implantation (by altering the endometrium) . . .”[1] While this change was highlighted by media outlets, the FDA also made other important changes to its published information about LNG-EC and the reasons therefor in its website page for Plan B One-Step[2] and Decisional Memorandum.[3] These changes include:

1. The FDA formally stated, much more explicitly than it ever did before, that LNG-EC does not “terminate a pregnancy” and does not act as an abortifacient (FDA Website).
2. The FDA removed any discussion of LNG-EC’s mechanism of action from the Drug Facts label on boxes of LNG-EC pills. Past labels had contained information about Plan B’s mechanism of action. Now, simplified language about mechanism of action (emphasizing LNG-EC’s impact on ovulation) is provided only in a Consumer Information Leaflet.
3. The FDA also retracted prior language that LNG-EC may prevent fertilization by altering tubal transport of sperm and/or ova.[4]

What Evidence and Arguments Did the FDA Provide for Its Action?

After providing background on the chemical nature of PBOS and LNG-EC (a 1.5 mg dose of the synthetic progestin Levonorgestrel) and of the typical events of early reproductive processes, the FDA summarized and defended its principal arguments in the course of a review of clinical research. The FDA argued that:

- LNG-EC inhibits or delays ovulation when administered prior to the lutenizing hormone (LH) surge;
- LNG-EC does not have a significant effect on cervical mucus quality or on sperm capacitation, motility, or quantity in the genital tract;
- When provided after ovulation, LNG-EC does not affect the endometrium in a clinically meaningful way to prevent implantation;
- When provided after ovulation, LNG-EC does not affect the expected rate of pregnancy (e.g., that which would be expected if LNG-EC were not provided).[5]

Examining the Sufficiency of the FDA’s Evidence and Arguments

While the FDA’s review of clinical research is well-organized and accurate and covers important facts about LNG-EC’s alleged mechanisms of action, it does not resolve important, valid concerns about a key mechanism of action when it is administered in the late follicular phase, that is, immediately before ovulation.

Are FDA Evidence and Arguments Ruling-Out LNG-EC Abortifacient Side Effects Convincing?

As noted above, the FDA stated more formally and explicitly than ever before that LNG-EC will not cause an abortion or act as an abortifacient. With regard to the issue of abortion, the FDA appears to be correct in stating that “Plan B One-Step will not work if a person is already pregnant, meaning it will not affect an existing pregnancy.”[6]

In addressing the question of whether Plan B One-Step acts as an abortifacient, it is important to note that the FDA’s focused narrowly on two things: (1) assessment of LNG-EC on endometrial tissue (in in vitro studies), and (2) on the difference between clinical pregnancy rates based on whether LNG-EC is administered before or after ovulation (note: the clinical pregnancy rates are determined by HCG test, a uniquely post-implantation event). The FDA explicitly cites 45 CFR 46.202 (“Pregnancy encompasses the period of time from implantation until delivery.”)[7] as its reference point for settling the issue of abortion and abortifacient side effects. This is significant because, if one counts as abortifacient action only those effects at or after implantation, then one is ignoring a critical period in early human life, the interval between fertilization and implantation. Biologically speaking, the existence of human life in this several-day period is indisputable. Ethically speaking, acting with the intent or means to destroy human life in this interval constitutes an abortifacient action.

However, the FDA did not address all of LNG-EC’s mechanisms of action—particularly

in cases where LNG-EC cannot and does not prevent ovulation—that appear to meaningfully impact the survival of human beings *after* fertilization and *prior* to implantation. As will be explained below, there is valid evidence for concern about such effects.

Are the FDA's Arguments about LNG-EC's Impact on Ovulation Convincing?

The FDA states that the sole mechanism of action for LNG-EC for which there is strong data is the delay or prevention of ovulation. In its section E of the Decisional memorandum, entitled “Integrated Summary of Current State of Knowledge Regarding Mechanism of Action of Levonorgestrel Emergency Contraception,” the FDA stated:

As discussed above, studies available prior to the 2003 review, including clinical studies by Landgren (1989), Durand (2001), and Marions (2002), showed that LNG suppressed the midcycle LH surge and suppressed ovulation. . . . Studies by Novikova (2007) and Noé (2011) provide the strongest clinical data that suppression of the midcycle LH surge and interference with ovulation are the main mechanisms by which LNG-EC prevents pregnancy.[8]

However, the FDA failed to discuss evidence demonstrating that LNG-EC's ability to suppress the mid-level LH surge and ovulation *diminishes* as ovulation approaches. A review of 11 clinical studies with data on this issue shows that, while LNG-EC can suppress ovulation at an average rate of 91 percent when given on Day -4 before ovulation, the average falls to 43 percent on Days -3 to -2 and to 8 percent on Days -1 to 0.[9] The FDA is well aware of these studies and cited one of them as providing some of the strongest clinical data for interference with ovulation as the main mechanism by which LNG-EC prevents pregnancy. [10] Yet Noé's study demonstrated that 80 percent of the women who received LNG-EC on Days -5 to -1 ovulated *in spite of the drug*. The relative (in)effectiveness of LNG-EC in suppressing ovulation based on the timing of its administration calls into question the FDA's contention that its sole mechanism of action is the delay or prevention of ovulation. At a minimum, providing women information about when LNG-EC can or cannot inhibit ovulation is essential for informed consent.

Does the FDA Adequately Consider Important Data Suggesting that LNG-EC Can Harm Humans Conceived after Administration of LNG-EC?

In addition to its questionable emphasis on LNG-EC's sole mechanism of action, the FDA fails to address evidence that LNG-EC can negatively impact human beings conceived after women take it. Evidence for a post-ovulatory effect of LNG-EC comes from the 2011 study from Noé et al.; again, the one that the FDA regards as providing particularly strong data. Granted, some relevant clinical data is not reported. But it is the best clinical research available. Data from the 2011 study from Noé et al. demonstrate that of 103 women who received LNG-EC and had sexual intercourse during Days -5 to -1, sixteen pregnancies would have been expected without LNG-EC and yet zero (0) pregnancies occurred.[11] As noted above, Noé's study showed that 80% of these 103 women ovulated even after taking LNG-EC. These realities are striking. That LNG-EC *both* fails to prevent ovulation and yet still prevents pregnancies strongly suggests that it has harmful effects on early human life after fertilization and prior to implantation. Noé explicitly mentioned this possibility in an earlier version of her paper in 2010. However, she provided no evidence for her hypothesis that LNG could impede the migration of

sperm by increasing cervical mucus viscosity, and clinical research reviewed in the FDA memorandum appears to rule this out. Neither Noé, nor anyone since, has provided clinical data to account for this anomaly, i.e., demonstrating how LNG-EC can still prevent fertilization when it fails to prevent ovulation.

The combination of LNC-EC's declining ability to prevent ovulation, along with its demonstrated ability to prevent pregnancies when given immediately prior to ovulation, calls into question the FDA's assertion that LNC-EC cannot act as an abortifacient. The FDA's argument and choice of terms may be influenced by its definition of pregnancy, as noted above. Yet even if one grants the FDA's choice of terminology, LNG-EC's impact when given immediately prior to ovulation can be described as potentially embryocidal. Therefore, there are valid reasons for concern about LNG-EC's impacts on early human life and for health care professionals to decline to administer LNG-EC when it may well have an embryocidal effect.

Are There Other Factors Shaping the FDA's Actions at this Time?

The FDA has twice rejected requests (in 2005 and 2010) to change its longstanding language regarding LNG-EC's potential impact on implantation. Since there were only three relevant clinical studies bearing on the mechanisms of action of LNG-EC since 2010, other factors might have shaped the FDA's action in December 2022. First, in its recent action the FDA spoke to the issue of abortion and abortifacient side effects of LNG-EC more formally and in stronger terms than it ever had before. Is it possible that the timing and content of the FDA decision was shaped by concerns stemming from the Supreme Court's overturning the landmark abortion case, *Roe v. Wade*? As early as June 2022, as concerns over the impending Supreme Court decision in the *Dobbs vs. Jackson Women's Health Organization* case began to rise,[12] commentators explicitly speculated on whether use of LNG-EC could be restricted in a post-*Roe* legal framework, in particular because of the FDA's existing language about its possible post-fertilization mechanisms. It is possible that the fevered political climate post-*Dobbs* helped to influence the timing and content of the FDA's decision. At issue is not that the FDA tried to resolve questions about LNG-EC's mechanism of action per se. Rather, one can question the timing and tenor of the FDA's actions given the absence of new research on the critical issue identified above—the ability of LNG-EC to prevent pregnancies without being able to prevent ovulation. For example, the Noé study mentioned above is over ten years old. If the FDA wanted to effectively dispel concerns about LNG-EC's post-fertilization mechanisms of action, it should have performed or required new clinical research.

Ensuring Ethical Integrity in Administering LNG-EC after Sexual Assault in Catholic Health Care

The moral principles guiding a compassionate, competent, and ethical response to victims of sexual assault are best captured in the *Ethical and Religious Directives for Catholic Health Care Services* (USCCB, 2018). Directive 36 states:

Compassionate and understanding care should be given to a person who is the victim of sexual assault. Health care providers should cooperate with law enforcement officials and offer the person psychological and spiritual support as well as accurate medical information. A female who has been raped should be able to defend herself against a potential conception from the sexual assault. If,

after appropriate testing, there is no evidence that conception has occurred already, *she may be treated with medications that would prevent ovulation, sperm capacitation, or fertilization. It is not permissible, however, to initiate or to recommend treatments that have as their purpose or direct effect, the removal, destruction, or interference with the implantation of a fertilized ovum.*[13] (emphasis added).

There are at least two significant goods at stake in responding to victims of sexual assault: (1) the good of the victim, which includes the right of defending herself against an attacker and against a potential fertilization resulting from sexual assault; and (2) the good, including the right to life, of a human conceived as a result of a sexual assault. There is a profound moral duty to avoid interventions that would cause the death of an innocent human being. In responding to female victims of sexual assault, Catholic health care institutions and professionals should strive to protect both goods. To implement Directive 36 with integrity, Catholic health care institutions and professionals should ensure with moral certitude that, at a minimum, LNG-EC is *not* dispensed when it most likely could not prevent ovulation but may cause the death of an embryo. An assessment should take place for each patient to discern whether this moral danger exists. That is, people should not rely on mere probabilities or averages regarding likelihood of pregnancies after sexual assault or on the overall effectiveness of LNG-EC. In the face of uncertainty, people should seek greater moral clarity. Efforts to assess the potential ovulatory status of victims of sexual assault should be improved over time as are other treatment protocols.

As noted in the preceding section, some have expressed concern that the availability of LNG-EC could be limited after the Supreme Court overturned *Roe v. Wade*. Conversely, some states may try to increase the availability of LNG-EC, in part to limit the demand for chemical or surgical abortion. In July 2022, Louisiana enacted a law requiring LNG-EC to be administered after a negative pregnancy test and upon patient request.[14] The law makes no provision for health care institutions or professionals to assess each victim appropriately prior to dispensing LNG-EC. However, even the motive to lessen chemical and surgical abortions does not justify denying professional judgment and religious liberty. Any legislation proposed to expand the availability of LNG-EC should ensure that the clinical judgment and religious liberty of health care professionals and institutions are respected.

Ethicists of The National Catholic Bioethics Center

[1] US Food and Drug Administration, “PlanB One-Step Package Labeling,” *FDA Access Data*, accessed January 30, 2023, https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/021998Orig1s005lbl.pdf.

[2] US Food and Drug Administration, “Plan B One-Step (1.5 mg levonorgestrel) Information,” *fda.gov*, last update December 23, 2022, <https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/plan-b-one-step-15-mg-levonorgestrel-information>.

[3] US Food and Drug Administration, “Decisional Memorandum: New Drug Application 21998, Supplement 5, Levonorgestrel 1.5 mg Tablet Emergency Contraceptive Labeling

Supplement for Update to Mechanism of Action Information,” *FDA Access Data*, December 23, 2022, https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/021998Orig1s005SumR.pdf.

[4] FDA, “Decisional Memorandum.”

[5] FDA, “Decisional Memorandum,” 1–2.

[6] FDA, “PlanB One-Step Package Labeling.”

[7] Public Welfare 45 C.F.R. 46.202 (2023).

[8] FDA, “Decisional Memorandum,” 19.

[9] Rebecca Peck et al., “Does Levonorgestrel Emergency Contraceptive Have a Post-Fertilization Effect? A Review of Its Mechanism of Action,” *Linacre Quarterly* 83.1 (February 2016): 38, doi: 10.1179/2050854915Y.0000000011.

[10] Gabriela Noé, “Contraceptive Efficacy of Emergency Contraception with Levonorgestrel Given before or after Ovulation,” *Contraception* 84.5 (November 2011): 486–493, doi: 10.1016/j.contraception.2011.03.006.

[11] Noé et al., “Contraceptive Efficacy.”

[12] Sarah Varney, “Future of America’s Most Popular Emergency Contraception is Complicated by Misinformation,” *CNN*, June 7, 2022, <https://www.cnn.com/2022/06/07/business/emergency-contraception-khn-partner-wellness/index.html>.

[13] US Conference of Catholic Bishops, *Ethical and Religious Directives for Catholic Health Care Services*, 6th ed. (Washington, DC: USCCB, 2018), dir. 36, emphasis added.

[14] Louisiana Act No. 513 (June 15, 2022).