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Supplement to Citizen Petition (Docket Number FDA-2025-P-1449) to Promptly Require an Explicit Pregnancy Contraindication and Related Labeling Changes for Modafinil and Armodafinil

May 18, 2026

Public Citizen, a consumer nonprofit advocacy organization with more than one million members and supporters nationwide, and Public Citizen's Health Research Group submit this supplement to our May 28, 2025, citizen petition to the Food and Drug Administration (FDA), which was assigned docket number FDA-2025-P-1449.[1] The original petition requested that the Commissioner of Food and Drugs promptly require contraindicating the use of the widely prescribed oral wakefulness-promoting drugs modafinil (PROVIGIL and generics) and armodafinil (NUVIGIL and generics) during pregnancy and in females of reproductive potential who are not using effective contraceptives. Additionally, we asked that boxed warnings be required for the labeling of both drugs to highlight their potential risk of embryofetal toxicity.

Recently, an industry-funded final analysis of data from an FDA-mandated U.S. registry (called the Nuvigil and Provigil Pregnancy Registry) found a fourfold higher rate of major congenital malformations among fetuses exposed to modafinil or armodafinil during pregnancy than in the general U.S. population,[2] supporting our original petition and corroborating earlier findings from this important registry.

As discussed below, the new analysis and the evidence outlined in our original petition make a strong case for why the FDA should promptly act on our petition.

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[1] Public Citizen. FDA Petition to require contraindicating use of modafinil (PROVIGIL and generics) and armodafinil (NUVIGIL) during pregnancy. May 28, 2025. https://www.citizen.org/wp-content/uploads/2735.pdf. Accessed May 14, 2026.

[2] Kaplan S, Carneal-Frazer N, Braverman DL, et al. Pregnancy and fetal outcomes following prenatal exposure to modafinil and/or armodafinil: A 14-year registry study. *Neurol Clin Pr*. 2025;15(6):e200551.

Summary of earlier evidence

Our 2025 petition described findings from animal studies that led FDA reviewers in 2007 to conclude that modafinil and armodafinil should be labeled as developmental toxicants and to recommend the establishment of the U.S. pregnancy registry for the two drugs.[3,4]

Moreover, the petition discussed post-marketing observational studies, including interim analyses of the U.S. pregnancy registry documenting higher rates of major congenital malformations among infants exposed to either of the two drugs during pregnancy. For example, a 2021 analysis found that 13% of 119 live births with prenatal exposure to modafinil or armodafinil involved major congenital malformations, compared with just 3% in the general U.S. population.[5] The malformations included torticollis (a condition involving contracted neck muscles that twist the head to one side) and hypospadias (a congenital condition in which the urethral opening is abnormally located in males).

Moreover, the rate of heart malformations among exposed live births was approximately 3%, compared with 1% in the general U.S. population.

Our original petition highlighted that the above evidence had already led regulators in several countries — including Australia, Canada, Ireland, and the United Kingdom — to require contraindications against the use of modafinil and armodafinil during pregnancy and in females who may become pregnant and are not using effective contraceptives, because the two drugs may decrease the effectiveness of hormonal contraceptives.

Final U.S. registry analysis

Published in the December 2025 issue of *Neurology: Clinical Practice*, the new registry analysis examined final data collected between February 2010 and January 2024. The analysis was funded by Teva, the former manufacturer of Provigil and Nuvigil.

A total of 191 pregnancies were enrolled in the registry.[6] These pregnancies were associated with the use of modafinil (49%), armodafinil (48%), both drugs (2%), or an undetermined one of these drugs (1%) during pregnancy or within six weeks prior to pregnancy. Enrollment was voluntary and initiated by the participants. The mean age of the participants was 31 years.

[3] Food and Drug Administration. Medical review, Part 1, NDA 21-875, armodafinil (Nuvigil). 2007. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021875s000_MedR_P1.pdf. Accessed May 14, 2026.
[4] Food and Drug Administration. Review and evaluation of pharmacology and toxicology (by J. Edward Fisher, Ph.D. et al.), armodafinil (Nuvigil), NDA: 21-875. 2006. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021875s000_PharmR.pdf. Accessed May 14, 2026.
[5] Kaplan S, Braverman DL, Frishman I, Bartov N. Pregnancy and fetal outcomes following exposure to modafinil and armodafinil during pregnancy. *JAMA Intern Med*. 2021;181(2):275-277.
[6] Kaplan S, Carneal-Frazer N, Braverman DL, et al. Pregnancy and fetal outcomes following prenatal exposure to modafinil and/or armodafinil: A 14-year registry study. *Neurol Clin Pr*. 2025;15(6):e200551.

The most frequent indications for prescribing either medication were narcolepsy (a rare chronic sleep disorder characterized by excessive daytime sleepiness, brief involuntary sleep episodes, and certain other symptoms) and idiopathic hypersomnia (a chronic sleep condition with an unknown cause characterized by severe, uncontrollable daytime sleepiness despite normal sleep duration).

Pregnancy and fetal outcomes were known for 179 pregnancies, which resulted in 188 fetuses. Of those fetuses, 156 (83%) were prospective (enrolled in the registry before the pregnancy outcome was known or a congenital malformation was detected through prenatal testing) and the remaining 32 (17%) were retrospective (enrolled after either the pregnancy outcome or a congenital malformation was known).

The 156 prospectively enrolled fetuses included 137 (88%) live births, 17 (11%) spontaneous abortions, and 2 (1%) elective pregnancy terminations. The median gestational age for spontaneous abortions was 9 weeks.

Of 156 prospectively enrolled fetuses exposed to modafinil or armodafinil at any time during pregnancy, 13% had major congenital malformations, a rate much higher than that of the general population. The malformations involved the musculoskeletal system, central nervous system, male genitalia, heart, cleft lip or palate, and other structural abnormalities, with some involving chromosomal anomalies.

Likewise, of the 137 prospectively enrolled live-birth fetuses exposed to modafinil or armodafinil at any time during pregnancy, 13% had major congenital malformations; the rate was 14% among those exposed during the first trimester. Moreover, 17% of the prospectively enrolled live-birth fetuses had at least one minor birth defect.

Conclusions

The Nuvigil and Provigil Pregnancy Registry is one of the largest available prospective data sources on exposure to modafinil or armodafinil during pregnancy, and analyses of its data have consistently demonstrated an increased risk of major congenital malformations associated with prenatal exposure to these drugs.

Yet the findings of this registry had not been incorporated into the U.S. labeling of the two drugs.[7,8] Instead, the current modafinil labeling continues to indicate that the drug "should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus," and armodafinil's medication guide continues to state that "[i]t is not known if [the drug] will harm [the] unborn baby."[9] The labeling of both drugs discusses animal studies and notes only that, based on these data, the two drugs *may* cause fetal harm.

[7] Apotex Corp. U.S. label: modafinil (PROVIGIL). February 2025. https://www.provigil.com/pdf/provigil-prescribing-information.pdf. Accessed May 14, 2026.
[8] Apotex Corp. U.S. label: armodafinil (NUVIGIL). February 2025. https://www.nuvigil.com/pdf/nuvigil-prescribing-information.pdf. Accessed May 14, 2026.
[9] Apotex Corp. U.S. medication guide: armodafinil (NUVIGIL). February 2025. https://www.nuvigil.com/pdf/nuvigil-medication-guide.pdf. Accessed May 14, 2026.

Therefore, it is imperative for the FDA to promptly follow the public health precautionary principle by mandating explicit pregnancy contraindication warnings in the labeling of modafinil and armodafinil to caution the public about the potential risk of major congenital malformations associated with the use of these drugs.

This is especially important given the extensive off-label use of modafinil and armodafinil, and the fact that nearly half of U.S. pregnancies are unplanned.[10]

Thank you for your consideration of this supplemental evidence and our original petition.

Sincerely,

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[10] Rossen LM, Hamilton BE, Abma JC, et al. Updated methodology to estimate overall and unintended pregnancy rates in the United States. National Center for Health Statistics. *Vital Health Stat* 2(201). 2023. https://www.cdc.gov/nchs/data/series/sr_02/sr02-201.pdf. Accessed May 14, 2026.