

202-638-3386



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-045/S-011

Barr Research, Inc.
Attention: Joseph A. Carrado, M.Sc., Ph.D.
Senior Director, Regulatory Affairs
One Bala Plaza, Suite 324
Bala Cynwyd, PA 19004-1401

Dear Dr. Carrado:

Please refer to your supplemental new drug application dated April 16, 2003, received April 22, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B® (0.75mg levonorgestrel) tablets.

We acknowledge receipt of your submissions dated July 25 (3) and 31, August 8 (2), September 4, 8, 9, and 15, October 6, 10, 15 (2), 17, 21, 24, 29, 30 and 31, December 3 and 9, 2003; and January 9 and 30, February 6, 10, 13, 20 and 24, and March 11 and 26, 2004.

This supplemental new drug application proposes nonprescription (over-the-counter (OTC)) availability of Plan B (0.75mg levonorgestrel) tablets for emergency contraception to reduce the chance of pregnancy after unprotected sex (if a contraceptive failed or if birth control was not used).

We have completed our review of this supplement and, for the reasons described below, find that the supplemental application is not approvable at this time under section 505(d) of the Act and 21 CFR 314.125(b).

You propose OTC status for Plan B for both adults and children based primarily on an actual use study in 585 subjects. Only 29 of the 585 subjects enrolled in the study were 14-16 years of age, and none was under 14 years of age.

In a December 16, 2003 joint meeting, the Nonprescription Drugs Advisory Committee and the Reproductive Health Drugs Advisory Committee considered your proposal to switch Plan B to nonprescription status. Although the Joint Committee recommended that your proposal to switch Plan B be approved, some members of the Joint Committee, including the Chair, raised questions concerning whether the actual use data were generalizable to the overall population of nonprescription users, chiefly because of inadequate sampling of younger age groups.

Based on a review of the data, we have concluded that you have not provided adequate data to support a conclusion that Plan B can be used safely by young adolescent women for emergency contraception without the professional supervision of a practitioner licensed by law to administer the drug. In your March 11, 2004, amendment, you proposed to change the indication to allow for marketing of Plan B as a prescription-only product for women

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under 16 years of age and a nonprescription product for women 16 years and older. This preliminary proposal did not include draft product labeling to demonstrate how you propose to comply with both the prescription and nonprescription labeling requirements in a single packaging configuration. Because of the preliminary and incomplete nature of the proposal, we did not conduct a complete review of this amendment during this review cycle.

Before this application can be approved, you would have to provide data demonstrating that Plan B can be used safely by women under 16 years of age without the professional supervision of a practitioner licensed by law to administer the drug. Alternatively, you could supply additional information in support of the revised indication to allow for marketing of Plan B as a prescription-only product for women under the age of 16 years and a nonprescription product for women 16 years and older, including draft product labeling. If you take the latter approach, your response to this letter would have to include details of how you propose to implement simultaneous prescription and nonprescription marketing of Plan B for women of different ages in a single packaging configuration while complying with all relevant statutory and regulatory requirements for labeling and marketing of this product. We will have to assure ourselves that your proposed approach is consistent with our statutory authority. If you pursue the alternative approach, we also would request details of your proposed program to educate consumers, pharmacists, and physicians about the dual marketing of Plan B as both a prescription and nonprescription product, as well as your proposed program to monitor implementation of this novel approach.

Wide availability of safe and effective contraceptives is important to public health. We look forward to continuing to work with you if you decide to pursue either of these options.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified,

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4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Divisions of Over-the-Counter Drugs and Reproductive and Urologic Drug Products to discuss what steps need to be taken before the application may be approved.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call the Regulatory Project Manager at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Steven Galson, M.D., M.P.H.
Acting Director
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Steven Galson
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