



MEDICAL OFFICER'S REVIEW

Department of Health and Human Services
Food and Drugs Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation (HFD-560)

NDA#:	21-998
Drug:	Single tablet levonorgestrel 1.5 mg (Plan B One-Step)
Dosage Form:	Tablet
Pharmacologic Category:	Progestogen
Sponsor:	Duramed
Indications:	Emergency contraception
Document:	Complete Response
Submission Date:	January 9, 2009
PDUFA Goal date:	July 12, 2009
Review Date:	July 6, 2009
Reviewer:	Christina Chang, M.D., M.P.H.
Team Leader:	Lesley Furlong, M.D.

1. Introduction

This is a DNCE medical officer's review of the proposed over-the-counter labeling submitted as part of the Complete Response (CR) to address a deficiency identified in FDA's Approvable Letter issued November 22, 2006. The Division of Reproductive and Urologic Products (DRUP) is the lead review division for the submission. The present review is confined to the OTC labeling.

Proposed labeling consists of Rx and OTC dual labeling similar to the two-dose levonorgestrel product (Plan B) except for dosing instructions. The application was amended on June 9, 2009, to propose inclusion of women 17 years of age for OTC marketing. The amendment also included a safety update for levonorgestrel.

The Division of Nonprescription Regulation Development (DNRD) and the Division of Drug Marketing, Advertising, and Communications (DDMAC) have also reviewed the proposed OTC labeling. The Division of Medication Errors Prevention and Analysis (DMEPA) reviewed the trade name.

2. Background

Plan B One-Step is similar to Plan B, the only OTC product currently marketed for emergency contraception. The dosing regimen for Plan B consists of two doses of 0.75 mg tablets taken 12 hours apart, with the first dose taken as soon as possible within 72 hours of intercourse. Plan B obtained prescription-only (Rx) status on July 28, 1999. During the review for the OTC switch of Plan B, then CDER Director, Dr. Steven Galson, concluded that the data provided would

support approval for OTC use for women 17 and older, but not for adolescents 16 and younger.¹ Dr. Andrew von Eschenbach, then Acting FDA Commissioner, concurred that the data supported approval for OTC use for women 17 and older, but concluded that, due to enforcement issues, the appropriate age for OTC access should be 18.² On August 24, 2006, FDA approved over-the-counter (OTC) marketing for women 18 and older, thus creating a unique dual-marketing distribution status.

Plan B One-Step is a single dose version of Plan B. On January 24, 2006, Duramed submitted NDA 21-998 to DRUP, proposing to market the single-dose regimen of 1.5 mg levonorgestrel as a prescription-only product. The 2006 application supported the safety of the single dose regimen with the results of two large clinical trials (N= 1,906 women in single dose treatment arms), and postmarketing data from an estimated (b) (4) sales of the single dose product in 27 countries. Following publication of the results of the two large clinical trials in 2002, experts in contraceptive technology began to recommend the off-label use of Plan B as a two-tablet, single dose regimen. FDA has monitored the postmarketing safety of Plan B since its approval in 1999, and Plan B continues to demonstrate satisfactory postmarketing safety.

In November 2006, the Agency determined that Plan B One-Step was safe and effective. However, because the related product, Plan B, was OTC for women aged 18 and older, the Agency also determined that Plan B One-Step, a simpler regimen, could be used safely and effectively as an OTC product by women aged 18 and older. Therefore, FDA took an Approvable Action on November 22, 2006. The deficiencies cited in the Action Letter were the need to submit:

- “revised labeling that meets the requirements of marketing of levonorgestrel tablets, 1.5 mg, as a prescription product for women 17 years of age and younger, and as a nonprescription product for women 18 years of age and older”
- “your plan regarding distribution of both the Rx and OTC versions of your product”

Duramed submitted a Complete Response to NDA 21-998 on January 9, 2009.

On March 23, 2009, United States District Court Judge Edward Korman issued an order directing the Agency to permit Duramed to make Plan B available to women 17 and older without prescription within 30 days. In addition, Judge Korman also ordered FDA to reconsider whether to approve Plan B for OTC status without age or point-of-sale restriction.

On April 21, 2009, Dr. Andrea Leonard-Segal, Director of FDA’s Division of Nonprescription Clinical Evaluation, sent a letter to Duramed concluding that Plan B may be made available to women 17 years and older without a prescription, and that Duramed could pursue the change in labeling by submitting revised draft labeling for review. In her letter, Dr. Leonard-Segal noted that the Agency had previously determined data supported the safety of Plan B as an OTC product for women 17 years or older. Furthermore, Dr. Leonard-Segal had considered the previous Acting Commissioner’s enforceability concerns and was unaware of data supporting a

¹ Memorandum by Dr. Steven Galson, dated August 26, 2005.

² Letter to Duramed from Dr. Andrew von Eschenbach, dated July 31, 2006

distinction between ages 17 and 18 in terms of enforceability of an age restriction. Finally, data submitted by Duramed from the Convenient Access Responsible Education (CARE) program supported the fact that pharmacists were able to check identification for the age restriction. Dr. Leonard-Segal concluded that Plan B may be made available to women 17 years and older without a prescription.

Medical officer comment:

I agree with Dr. Leonard-Segal's conclusion that Plan B may be made available to women 17 and older without a prescription. I also believe that this conclusion can be applied to Plan B One-Step.

Following Judge Korman's order, Duramed met with the Agency on June 1, 2009, and stated their intention to pursue dual labeling with OTC access for women aged 17 and older by submitting amendments to both Plan B and Plan B One-Step. The revised labeling for Plan B One-Step was submitted on June 9, 2009.

3. Review of Submission

Safety Update

Duramed submitted a safety update on levonorgestrel used as an emergency contraception in the June 9, 2009 amendment. The content is currently under review in DRUP. At the time of this review, no new safety concerns had been detected.

Trade name

DMEPA objects to the trade name "Plan B ^{(b)(4)}," citing concern for increased confusion with Plan B resulting in medication errors. The second trade name proposed by the sponsor, "Plan B One-Step," is acceptable to DMEPA.

Findings relevant from NDA 21-045 (Plan B), supplement-011 for OTC switch

1. All reviewers up to the level of Center Director (Dr. Galson) concluded that data submitted by the sponsor met the statutory standard for approval for women 17 years and older.
2. The joint session of the Nonprescription Drug Advisory Committee and Advisory Committee of the Reproductive and Urologic Drugs voted overwhelmingly in favor of the Rx-to-OTC switch without age restriction:

Question: Are the Actual Use Study data generalizable to the overall population of potential non-Rx users of Plan B?

Yes = 27 No = 1

Question: Do you recommend Plan B be switched from prescription to non-prescription status?

Yes = 23 No = 4 (one member left before voting)

3. The Label Comprehension Study conducted in support of Plan B OTC switch enrolled 656 subjects.³ Of these, 355 women (54.1%, 355/656) were ages 17 to 25 years. This group met all communication objectives (90% to 96% correct or acceptable).
4. The Actual Use (AU) Study conducted in support of Plan B OTC switch enrolled 585 women aged 14 to 44 years.⁴ These women received one pack of Plan B at enrollment, and 540 (92%) used Plan B during the study. Of the 585 women enrolled, 556 (95.0%) were ages 17 to 44 years; 518 out of these 556 (93.2%) actually took Plan B. The pertinent results from the AU study for this age group are as follows:

Overall correct use	68.5%
Correct use of the first pill (< 72 hours)	90.5%
Correct use of the second pill (12 hours after the first pill)	73.7%

There were no serious adverse events reported, nor were new safety signals identified in this four-week study.

Medical officer comment:

With Plan B One-Step having a simpler dosing regimen than Plan B (one dose rather than two), it would appear reasonable to expect women 17 years and older to have a high percentage (at least 90%) of correct use of Plan B One-Step.

Consumer studies conducted in support of Plan B One-Step OTC status

1. A Label Comprehension Study was conducted by independent investigators whose findings were published in 2009.⁵ Since Duramed supplied only the prototype labeling without sponsoring the study, Duramed does not have access to raw data from the study. According to the publication, 171 adolescents aged 15 to 17 years participated in the study. A high proportion of this group understood five of the six key concepts tested (94% to 98%). Although the proportion of these adolescents scored lower on one key concept having to do with optimal timing for taking Plan B One-Step (Levonorgestrel 1.5 should be taken as soon as possible after sex, 86% correctly understood), a high proportion correctly understood the 72-hour time frame (Levonorgestrel 1.5 should be taken within 72 hours after sex, 98%). The authors interpreted this discrepancy to possibly the adolescents' tendency for more concrete cognitive pattern. Therefore, the authors suggested that combining the two instructions pertinent to timing of administration such as: "Levonorgestrel 1.5 should be taken as soon as possible after unprotected sex but not more than 72 hours later," may be helpful to the more literal-minded adolescents.

³ Label Comprehension Study review, Dr. Karen Lechter & Dr. Toni Piazza Hepp, dated November 5, 2003.

⁴ DNCE Medical Officer NDA review, Dr. Jin Chen, dated January 12, 2004.

⁵ Raymond EG, L'Engle KL, Tolley EE, Ricciotti N, Arnold MV et al. Comprehension of a prototype emergency contraception package label by female adolescents. *Contraception* 2009; 79: 199-205.

Medical officer comment:

*The proposed OTC label for women 17 years of age and older appears to have incorporated this recommendation by stating under **Directions**:*

“Take Plan B One-Step as soon as possible within 72 hours (3 days) after unprotected sex.”

2. Duramed has also initiated an Actual Use Study in adolescents 11 to 17 years of age. However, since Plan B One-Step remains an investigational product, enrollment into the AU study has been slower than anticipated.

CARE Program

When Plan B was approved approximately three years ago, the CARE program was put in place to check if pharmacists were able to follow the prescription age requirements of Plan B. The CARE program also had marketing components to increase knowledge about Plan B. Annual reports of the CARE program have been reviewed by DRUP, most recently for the year 2008. Compliance with the age restriction remains excellent (94%) at over 400 monitored pharmacies in 10 states, and the DRUP reviewer has recommended that the program is no longer necessary.

Medical officer comment: The CARE program has shown that pharmacists have adhered to the dual Rx-OTC labeling of the related product, Plan B. I concur with the DRUP reviewer who has stated that the CARE program is not necessary for the safe use of Plan B. As labeling and packaging of Plan B One-Step will be almost identical except for simpler dosing instructions, a CARE program is unnecessary for Plan B One-Step as well.

Labeling

1. The sponsor proposed under **Directions**: (b) (4)

Medical officer comment:

Following discussion within DNCE as well as with DRUP, we are recommending the following: “Prescription only for women younger than 17 years of age. If you are younger than 17 years of age, see a healthcare professional.”

2. Duramed proposed the following instruction under **Directions** (in the Consumer Information Leaflet) to women should vomiting occur after taking Plan B One-Step:

- (b) (4)

Medical officer comment:

The proposed two-hour time frame is based on the Tmax of Plan B (1.67 hours). This pharmacokinetic information led the World Health Organization expert Working Group to consider two hours sufficient for hormone absorption with no further action necessary if a woman vomits after this time.⁶ However, Duramed acknowledged in the submission that the company has not conducted any studies to determine the appropriate management should

⁶ Selected Practice Recommendations for Contraceptive Use, Second Edition: World Health Organization, 2004.

vomiting occur after taking Plan B or Plan B One-Step. Neither development plan collected efficacy or safety data at 2 hours.

Some providers may recommend repeating the dose (with or without an antiemetic), while others may not. Other management options may include another post-coital contraceptive (such as an intrauterine device). Thus, it is unclear what the optimal management option may be.

Furthermore, currently approved Plan B label directs the consumers to call a healthcare professional if vomiting occurs within 1 hour of taking either dose of the medication. The sponsor now proposes the 2 hour limit for Plan B as well as for Plan B consumers to repeat the dose after vomiting. There is concern that women may not understand when the second dose should be taken if the first dose is repeated due to vomiting. This newly proposed direction was not assessed in the Label Comprehension Study conducted to support the Plan B application. Given that both Plan B and Plan B One-Step will be marketed simultaneously, it would be prudent to have consistent language for both regimens to minimize confusion.

Again, following internal discussion, we recommend the following for Plan B One-Step Consumer Information Leaflet:

“If you vomit within 2 hours of taking the medication, call a healthcare professional to find out if you should repeat the dose.”

3. The DDMAC reviewer noted a number of promotional statements in the consumer leaflet and recommended removal of the statements. The DNRD and DNCE labeling team concurred with removing promotional statements from the consumer leaflet.
4. The package insert for the prescription version Plan B One-Step notes that there was an increased rate of pregnancy among Chinese women in the Plan B One-Step trial. However, the prescription package insert does not limit Plan B to certain racial groups. The DRUP review of the data stated that the pregnancy rate among Chinese women in the Plan B One-Step trial was 1.50%, whereas the pregnancy rate among non-Chinese women was 1.44%. The difference was not statistically significant. The clinical significance, if any, of the difference in point estimates of the pregnancy rates for Chinese and non-Chinese women is unknown.

Medical officer comment:

Because it is unlikely that the information about possible racial differences in efficacy would have any utility to the consumer, the information is unnecessary on the OTC label.

5. Based on postmarketing information from Plan B, the sponsor has proposed adding two new adverse events – dysmenorrhea and pelvic pain –to the Adverse Reaction section of Plan B prescription label. DRUP has requested that similar information be added to the Postmarketing Experience section of the Plan B One-Step label as well.

Medical officer comment:

According to Dr. Daniel Davis' review⁷, dysmenorrhea and pelvic pain occurred with very rare frequencies (< 1/10,000) in the postmarketing experience of Plan B. These two events are covered by the broader term "lower abdominal pain" already in the OTC label. Therefore, I do not recommend the inclusion of either "dysmenorrhea" or "pelvic pain" in the OTC list of side effects.

6. There are minor differences between the most common adverse events listed for Plan B and those listed for Plan B One-Step. For example, the list of side effects for Plan B includes vomiting and diarrhea, whereas the list for Plan B One-Step does not. This reflects the types and frequencies of adverse events from different clinical trials.

Medical officer comment:

The two products are sufficiently similar that it would be ideal for the OTC labels to present identical side effect profiles so as to avoid confusion for the OTC consumers.

*Since nausea is the second most common side effect reported for both products, it would be reasonable to include vomiting in the list of common side effects for both products, despite the relatively low reporting frequency in the development of Plan B One-Step. Including "vomiting" as a side effect is also desirable because the label for Plan B One-Step includes instructions to the consumers (under **Directions**) should vomiting occur.*

On the other hand, (b) (4) may be deleted from the list of side effects from both products. The use of progestins is usually associated with decreased gastrointestinal motility, rather than the opposite. Furthermore, the reported frequencies of "diarrhea" were lower (5% in the original Plan B trial⁸, 4% in the Plan B One-Step trial⁹) than the other side effects in the OTC list.

4. Conclusions

1. Duramed has satisfactorily resolved the labeling deficiency specified in the Approvable Action Letter dated November 22, 2009.
2. Data required to expand the OTC population to include women 17 years of age were already included in the original application of NDA 21-998 as well as in NDA 21-045.
3. The CARE program is not necessary for the safe use of either Plan B or Plan B One-Step.

5. Recommendations

Pending successful labeling discussion with the sponsor, this reviewer recommends approval of Plan B One-Step with an OTC label for women who are 17 years of age and older.

⁷ Clinical Review, Complete Response to November 22, 2006 Action Letter, Dr. Daniel Davis.

⁸ Current Plan B label.

⁹ Clinical Review NDA 21-998, Dr. Daniel Davis, dated November 22, 2006.

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/s/

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I concur with Dr. Chang's conclusions and recommendations.