DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Mr. Joseph Carrado
Senior Director, Regulatory Affairs
Barr Research, Inc.
One Bala Plaza, Suite 324
Bala Cynwyd, PA 19004-1401

Re: NDA #21-544
Seasonale® (levonorgestrel/ethinyl estradiol) Tablets
MACMIS ID #12748

Dear Mr. Carrado:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a direct-to-consumer (DTC) television advertisement (TV ad) entitled "Yes" (1BARCON0173) for Seasonale® (levonorgestrel/ethinyl estradiol) Tablets submitted by Barr Research, Inc. (Barr) under cover of Form FDA 2253. The TV ad is false or misleading because it fails to reveal material facts about Seasonale and minimizes the risks associated with Seasonale, in violation of the Federal Food, Drug and Cosmetic Act ("Act") and FDA implementing regulations. See 21 U.S.C. §§ 352(n), 321(n); 21 CFR §§ 202.1(e). By omitting and minimizing the risks associated with Seasonale, the TV ad misleadingly suggests that Seasonale is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Background

According to the FDA-approved labeling (PI), Seasonale is an extended-cycle oral contraceptive consisting of 84 pink active tablets, each of which contains 0.15 mg of levonorgestrel, a synthetic progestogen, and 0.03 mg of ethinyl estradiol, and 7 white inert tablets (without hormones). The PI states that the dosage of Seasonale is one pink (active) tablet daily for 84 consecutive days, followed by 7 days of white (inert) tablets.

The Warnings section of the PI states, in part:

> The use of oral contraceptives is associated with increased risk of several serious conditions including venous and arterial thrombotic and thromboembolic events (such as myocardial infarction, thromboembolism, and stroke), hepatic neoplasia, gallbladder disease, and hypertension. The risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as certain inherited thrombophilias, hypertension, hyperlipidemias, obesity and diabetes.

With respect to bleeding irregularities, the Warnings section further states (emphasis added):

> When prescribing Seasonale®, the convenience of fewer planned menses (4 per year instead of 13 per year) should be weighed against the inconvenience of increased intermenstrual bleeding and/or spotting.
>
> The clinical trial (SEA 301) that compared the efficacy of Seasonale® (91-day cycles) to an equivalent dosage 28-day cycle regimen also assessed intermenstrual bleeding. The participants in the study were composed primarily of women who had used oral contraceptives previously as opposed to new users. Women with a history of breakthrough bleeding/spotting ≥ 10 consecutive days on oral contraceptives were excluded from the study. More Seasonale® subjects, compared to subjects on the 28-day cycle regimen, discontinued prematurely for unacceptable bleeding (7.7% [Seasonale®] vs. 1.8% [28-day cycle regimen]).
>
> Table 4 shows the percentages of women with ≥ 7 days and ≥ 20 days of intermenstrual spotting and/or bleeding in the Seasonale® and the 28-day cycle treatment groups.
>
> Table 4. Percentage of Subjects with Intermenstrual Bleeding and/or Spotting

Days of intermenstrual bleeding and/or spotting	Percentage of Subjects*	
Seasonale®	Cycle 1 (N=385)	Cycle 4 (N=261)
≥ 7 days	65%	42%
≥ 20 days	35%	15%
28-day regimen	Cycles 1-4 (N=194)	Cycles 10-13 (N=158)
≥ 7 days	38%	39%
≥ 20 days	6%	4%

> * Based on spotting and/or bleeding on days 1-84 of a 91 day cycle in the Seasonale subjects and days 1-21 of a 28 day cycle over 4 cycles in the 28-day dosing regimen.
>
> Total days of bleeding and/or spotting (withdrawal plus intermenstrual) were similar over one year of treatment for Seasonale® subjects and subjects on the 28-day cycle regimen.

In addition, the approved patient labeling that you disseminate with Seasonale includes similar warnings regarding intermenstrual bleeding and irregular spotting. For example, the "Detailed Patient Labeling" section entitled "Side Effects of Oral Contraceptives" states (emphasis added):

> Irregular vaginal bleeding or spotting…is likely to occur while you are taking Seasonale®. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Irregular bleeding occurs most often during the first few 91-day cycles of Seasonale® use, tends to decrease during later cycles, but may also occur after you have been taking Seasonale® for some time…

When you take Seasonale®, you need to consider the convenience of fewer expected menstrual periods (4 per year instead of 13) and the inconvenience of more irregular vaginal bleeding or spotting. In a clinical trial comparing Seasonale® (91-day cycles) to a conventional equivalent dosage 28-day cycle oral contraceptive, more women using Seasonale® discontinued treatment because of bleeding problems (7.7% of the Seasonale® users compared to 1.8% of the 28-day cycle users).

In addition, the "Brief Summary Patient Package Insert" under the heading entitled "**What You Should Know About Your Menstrual Cycle When Taking Seasonale®**" states (emphasis added):

When you take Seasonale®, which has a 91-day treatment cycle, you should expect to have 4 menstrual periods per year…However, you should expect to have more bleeding or spotting between your menstrual periods if you were taking an oral contraceptive with a 28-day treatment cycle. During the first Seasonale® treatment cycle, about 1 in 3 women may have 20 or more days of unplanned bleeding or spotting…This bleeding or spotting tends to decrease during later cycles. Do not stop Seasonale® because of the bleeding. If the spotting continues for more than 7 consecutive days or if the bleeding is heavy, call your healthcare provider.

Prior Written Communications from DDMAC
(b)(4)

Failure to Reveal Material Facts

The Seasonale TV ad states:

- "What if someone told you there was a new possibility in birth control pills?"
- "That now there's a daily pill that lets you have just four periods a year?"

These statements are reinforced by prominent graphics, a screen-filling SUPER ("**4 PERIODS a YEAR**"), and voiceovers that repeatedly state "four periods a year." They are further reinforced by the repeated use of both a graphic of a cluster of four pink circles and images of women wearing white dresses and pants. The TV ad thus claims that women who use Seasonale have only four periods a year.

The TV ad is misleading because it fails to reveal facts that are material in light of these claims. Specifically, it fails to reveal that (a) patients using Seasonale may experience breakthrough bleeding or spotting for up to a year, (b) the breakthrough bleeding may be up to the amount similar to a regular period, and (c) the total days of bleeding and spotting are similar in number for Seasonale subjects as for those on conventional oral contraceptives.

The only statements in the TV ad that refer to breakthrough bleeding minimize its extent and duration (emphasis added):

- "Initially there may be more breakthrough bleeding than with a monthly cycle pill." (SUPER)
- "Initially on Seasonale you're more likely to have breakthrough bleeding between periods than with a monthly cycle pill." (voiceover)

These statements misleadingly suggest that women should be concerned about "breakthrough bleeding" only at the beginning of using Seasonale, and that, with continued use of Seasonale, the risk of breakthrough bleeding will diminish substantially. However, according to the Warnings section of the PI, 42% of women reported 7 or more days and 15% reported 20 or more days of intermenstrual bleeding and/or spotting during cycle 4 of Seasonale, which roughly corresponds to the 10th through 12th month of treatment.

Furthermore, the ad fails to reveal that this breakthrough bleeding can be a "flow much like a regular period."

Moreover, the comparison in the ad to monthly cycle pills is misleading because it fails to reveal the material fact that total days of bleeding were similar over one year of treatment for Seasonale subjects and subjects on a conventional monthly cycle pill.

Minimization of Risk

The TV ad states:

> "Four periods a year…You're thinking, 'Is that really okay?'…Women's healthcare experts agree it is. Plus Seasonale is FDA approved."

The TV ad thus suggests that there is a consensus among medical experts that there are no adverse health effects of having only four periods a year. In fact, as discussed in the PI, Seasonale is associated with numerous risks, including the potentially serious risks of thromboembolic events and hypertension.

In addition, the risk information that is presented in the ad is minimized by the compelling visuals, fast-paced scene changes, and other competing modalities, such as background music and SUPERs, occurring simultaneously during the presentation of risk information in the TV ad. This complex presentation distracts from and makes it difficult for consumers to process and comprehend the important risk disclosures. Specifically, during the approximately 17 seconds of auditorily-presented risk information, the camera: pans multiple faces; shows a billowy cloth floating across the screen; presents many pink dots swirling quickly across the screen; cuts quickly to women's faces, body parts, pink dots, and a woman walking across the screen; and shows, again with quick cut camera work, two women throwing pink dots. This frenetic activity sequence occurs with shifting camera perspectives while complex contextual information and other unrelated informational elements are presented in subtitled SUPERs. Additionally, the SUPERs containing important contextual information are presented in small type as two lines of text at the bottom of the screen, rendering them extremely difficult to read under normal conditions, much less conditions under which they are presented against moving backgrounds and with overlying music. The overall effect of the distracting visual elements

and the competing audio message is to obscure and undermine the communication of the important risk information, minimizing these risks and misleadingly suggesting that Seasonale is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Conclusion and Requested Action

The TV ad fails to reveal material facts about Seasonale and minimizes the risks associated with Seasonale. Accordingly, the TV ad misbrands Seasonale in violation of the Act and FDA implementing regulations. See 21 U.S.C. § 352(n), 321(n); 21 CFR §§ 202.1(e).

DDMAC requests that Barr immediately cease the dissemination of promotional materials for Seasonale that are the same as or similar to those described above. Please submit a written response to this letter on or before January 12, 2005 describing your intent to comply with this request, listing all promotional materials for Seasonale that contain claims that are the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Room 8B-45, 5600 Fishers Lane, Rockville, MD 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to MACMIS ID #12748 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Seasonale comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Kay A. Chitale, Pharm.D.
Consumer Promotion Analyst
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

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

/s/

Kay Chitale

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