



TRANSMITTED BY FACSIMILE

Nancy Konnerth
Associate Director, Advertising and Labeling
Drug Regulatory Affairs
Berlex Laboratories
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

RE: NDA 21-098
Yasmin (drospirenone/ethinyl estradiol) Tablets
MACMIS ID# 11730

Dear Ms. Konnerth:

This letter notifies Berlex Laboratories (Berlex) that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified a direct-to-consumer (DTC) broadcast advertisement (TV ad) for Yasmin (drospirenone/ethinyl estradiol) Tablets that is misleading and in violation of the Federal Food, Drug, and Cosmetic Act (Act) and applicable implementing regulations. Specifically, the 60-second TV ad entitled "Goodbye Kiss" is misleading because it makes implied clinical superiority claims to other combination oral contraceptives and minimizes the important risk information that distinguishes Yasmin from other combination oral contraceptives. As a result, the TV ad raises significant public health and safety concerns.

Background

Yasmin is a combination oral contraceptive ("COC" or "birth control pill") prescription drug product. Yasmin, like any oral contraceptive, is associated with increased risks of several serious conditions (including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, gallbladder disease, and hypertension), although 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 hypertension, hyperlipidemias, obesity, and diabetes. (See the WARNINGS section of the Yasmin approved physician labeling (PI))

Yasmin contains the estrogen ethinyl estradiol and the progestin drospirenone. Drospirenone has antimineralocorticoid properties, which means that it can work against the body's normal mechanism for regulating salt and water balance, a situation that can lead to hyperkalemia in high risk patients, resulting in potentially serious heart and health problems. This additional risk is described in the Bolded Warning of Yasmin's PI:

Yasmin contains 3 mg of the progestin drospirenone that has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone [a potassium-sparing diuretic]. Yasmin should not be used in patients with conditions that predispose to hyperkalemia (i.e., renal insufficiency, hepatic dysfunction and adrenal insufficiency). Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium, should have their serum potassium level checked during the first treatment cycle. Drugs that may increase serum potassium include ACE inhibitors, angiotensin -- II receptor antagonists, potassium-sparing diuretics, heparin, aldosterone antagonists, and NSAIDs.

Consequently, Yasmin can exacerbate serious heart and health problems, in addition to the potential problems common to all COCs. Women taking Yasmin must be concerned about drug interactions that will increase potassium, in addition to the drug interactions common to all COCs. Therefore, these women and their healthcare providers must weigh Yasmin's additional health risks when considering Yasmin over COCs without drospirenone.

Misleading Efficacy and Safety Presentations

Prescription drug ads are false or misleading if they contain a drug comparison that represents or suggests that a prescription drug is more effective or safer than another drug when it has not been demonstrated to be safer or more effective by substantial evidence or substantial clinical experience (21 CFR 202.1(e)(6)(ii)). The TV ad misleadingly overstates the efficacy and safety of Yasmin by suggesting that Yasmin is unique and therefore clinically superior to other birth control pills because it contains the chemically different progestin drospirenone. The unifying theme of the ad, typified by the tagline "Ask about Yasmin, and **the difference a little chemistry can make**" (emphasis added) suggests that Yasmin is better than other birth control pills because of drospirenone and the way in which it is metabolized in the body. This "chemistry" difference is presented as a product benefit. FDA is not aware of substantial evidence or substantial clinical experience demonstrating that Yasmin is superior to other COCs or that the drospirenone in Yasmin is clinically beneficial. On the contrary, FDA is aware of the added clinical risks associated with drospirenone as communicated in the Warnings/Bolded Warning, and Precautions/Drug Interactions sections of the PI.

Specifically, the following claims in the TV ad address Yasmin's efficacy: "You don't settle when it comes to the guy...so why settle when it comes to the pill? **The Yasmin birth control pill uses a different kind of hormone. One that may work with your body chemistry.** Yasmin is over 99% effective at preventing pregnancy. So when you're looking for the right pill, ask your doctor about the difference a little chemistry can make." (emphasis added) These claims are misleading because they suggest that Yasmin's "different kind of hormone" offers unique "chemistry" benefits and that this difference contributes to the high rate of drug efficacy. Moreover, these claims are misleading because they imply superiority to other COCs (and thus do not offer the same product benefits as Yasmin Tablets) when such has not been demonstrated by substantial evidence or substantial clinical experience. Finally, these claims are misleading because they misrepresent Yasmin's mechanism of action by stating that Yasmin "uses a different kind of hormone. One that may work with your body

chemistry." However, COCs, including Yasmin, prevent ovulation by working against the usual body chemistry of a woman of childbearing potential by suppressing endogenous gonadotropins and, thereby, inhibiting ovulation and altering other changes associated with the menstrual cycle.

In addition, the statement "Yasmin contains a different progestin, which may increase potassium" is misleading because the "may increase potassium" disclosure fails to communicate that the potential to increase potassium is a risk. Furthermore, consumers may interpret the statement as a product benefit claim rather than a risk disclosure due to the overall positive message that Yasmin's "chemistry" is a product benefit. The ad conveys this positive message to consumers, notwithstanding the disclosure that "You should not take Yasmin if you have kidney, liver, or adrenal disease," because the "different kind of hormone" and "chemistry" messages are never clearly identified as potentially leading to increased potassium levels or that increased serum potassium can be dangerous. This important risk information is in a Bolded Warning in the PI and clearly conveyed in the Yasmin Brief Summary Patient Package Insert and in the Detailed Patient Package Insert:

Yasmin is different from other birth-control pills because it contains the progestin drospirenone. Drospirenone may increase potassium. Therefore, you should not take Yasmin if you have kidney, liver, or adrenal disease because this could cause serious heart and health problems. Other drugs may also increase potassium. If you are currently on daily, long-term treatment for a chronic condition with any of the medications below, you should consult your healthcare provider about whether Yasmin is right for you, and during the first month that you take Yasmin, you should have a blood test to check your potassium level.

Thus, by failing to add the necessary context to clarify that increased blood potassium is a safety risk rather than a clinical benefit, the ad misleadingly represents or suggests that Yasmin is safer than has been demonstrated by substantial evidence or substantial clinical experience.

In summary, the TV ad not only misleads consumers about the efficacy of Yasmin, the ad also minimizes important context about the health risks of the drug.

Conclusions and Requested Actions

Berlex should immediately discontinue the TV ad and all other promotional materials and activities for Yasmin that contain the same or similar violative presentations. Berlex should submit a written response to DDMAC on or before July 24, 2003, describing its intent and plans to comply with the above. In its letter to DDMAC, Berlex should include the date on which these and other similarly violative materials were discontinued.

Berlex should direct its response to the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857.

Nancy Konnerth.
Berlex Laboratories
NDA 21-098

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In all future correspondence on this matter, please refer to MACMIS ID# 11730 as well as the NDA number. DDMAC reminds Berlex that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Joan Hankin
Consumer Promotion Analyst
Division of Drug Marketing,
Advertising, and Communications

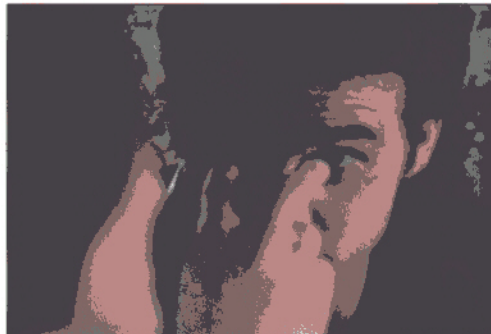
**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Joan Hankin
7/10/03 03:40:53 PM

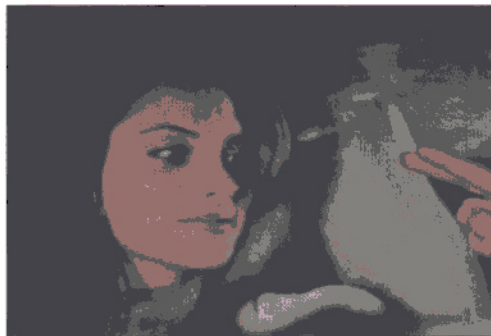
5/16/03

Directors Note: This commercial is all about showing the chemistry between two people. We use the wrong guy to demonstrate how special it is when you find the right guy. When we reveal the Yasmin girl finally finding the right guy, the goal is to play up the drama of the chemistry between them.



MALE 1:

I felt a real connection tonight.





ANNCR 1:

You don't settle when it comes to the guy...



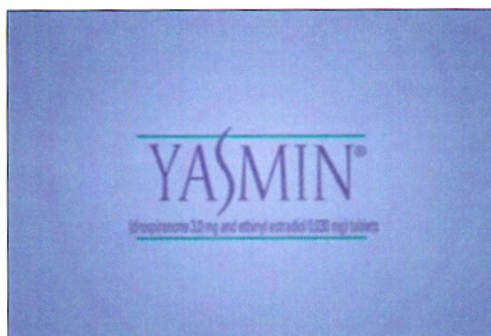
MALE 2:

You rock, babe!

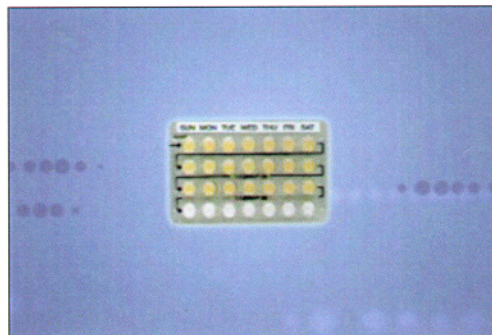


ANNCR 1:

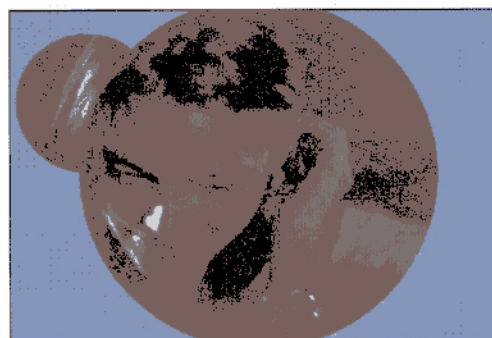
..so why settle when it comes to the pill?



The Yasmin birth control pill uses
a different kind of hormone.
One that may work with your body chemistry.



Yasmin is over 99% effective at preventing pregnancy,



So when you're looking for the right pill,



Ask your doctor about the difference
 a little chemistry can make.



ANNCR 2:

Yasmin contains a different progestin, which
 may increase potassium.
 You should not take Yasmin if you have
 kidney, liver or adrenal disease.

YASMIN®
drospirenone 3.0 mg and ethinyl estradiol 0.020 mg tablets

"Goodbye Kiss" :60 5/14/03
pg. 4 of 4



See our ad in Cosmopolitan

Tell your doctor if you are on daily,
long-term treatment with NSAIDs



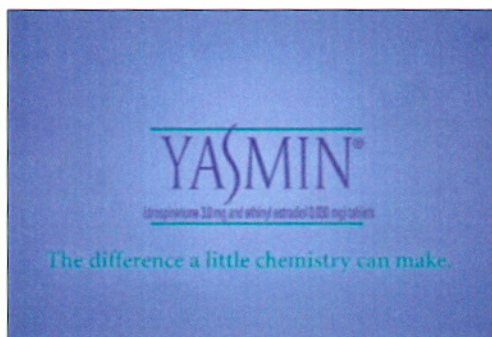
Visit our website www.yasmin.com

like Ibuprofen or Naproxen for a chronic
condition like arthritis, or taking
cardiovascular medications, or Heparin.
Birth control pills do not protect against HIV
or sexually transmitted diseases.



Call 1-888-YASMIN-1

Women especially over 35 should not smoke.
Serious risks, occurring infrequently,
include blood clots, stroke and heart attack.



ANNCR 1:

Ask about Yasmin, and the difference a little
chemistry can make.