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SUPERIOR COURT OF THE STATE OF CALIFORNIA

COUNTY OF SAN DIEGO

THE PEOPLE OF THE STATE OF CALIFORNIA, Plaintiff, v. **BAYER CORPORATION,** Defendant.	GIC 878812 **STIPULATION FOR MODIFICATION OF FINAL JUDGMENT and [PROPOSED] ORDER** Judge: Dept: 25

Plaintiff, the People of the State of California ("the People" or "Plaintiff"), having filed its complaint and appearing through Edmund G. Brown Jr., Attorney General of the State of California, by Frances Grunder, Senior Assistant Attorney General; Albert Norman Shelden, Special Assistant Attorney General; Catherine Ysrael, Supervising Deputy Attorney General; and Judith Fiorentini, Deputy Attorney General; and defendant Bayer Corporation ("Bayer" or "Defendant") appearing individually and through its attorneys, Sidley Austin LLP by Kristin Graham Koehler; DLA Piper LLP (US) by Christopher M. Young; and George J. Lykos, Chief

Legal Officer of Bayer Corporation, enter into this Stipulation for Modification of Final Judgment (hereafter "Modification") in this matter, which was originally entered on January 23, 2007; and

Plaintiff and Defendant further stipulate as follows:

1. This Court has jurisdiction over the subject matter of this case and of the parties consenting hereto.

2. Venue is proper as to all parties in this Court.

3. Plaintiff and Defendant aver that there have been no other modifications to the Final Judgment entered by this Court on January 23, 2007, a copy of which is attached hereto as Exhibit 1.

4. Defendant Bayer enters into this Modification solely for the purpose of resolving the investigation by the Modification Signatory Attorneys General, as defined in Paragraph 6.a.i. below, under both the Final Judgment and their respective state consumer protection statutes, into the issues identified in the Warning Letter issued by FDA's Division of Drug Marketing, Advertising, and Communications ("DDMAC") dated October 3, 2008 (attached as Exhibit 2 and hereafter referred to as "Warning Letter"), and to avoid unnecessary expense, inconvenience, and uncertainty, but without admitting any violation of the Final Judgment or state consumer protection statutes, and without admitting any wrongdoing and for settlement purposes only.

5. This Modification is made without adjudication of any issue of fact or law or finding of wrongdoing or liability of any kind. It is the intent of both Bayer and the Modification Signatory Attorneys General that this Modification shall not be admissible in any other matter or proceeding, and shall not bind Bayer in any respect other than in connection with the enforcement of this Modification. Except in an action by the Modification Signatory Attorneys General to enforce this Modification, this Modification shall not be construed or used as a waiver or limitation of any defense otherwise available to Bayer or of Bayer's right to defend itself, or make

arguments, in any other matter related to the issues identified in the Warning Letter.

6. The Final Judgment entered on January 23, 2007 remains in full force and effect. In addition to the terms contained therein, the Final Judgment is modified by written agreement of the Parties, to add the following terms as set forth below which shall be incorporated into the Final Judgment by this reference as though set forth fully therein:

a. Section I. Definitions is modified to add Paragraphs X and Y as follows:

i. Paragraph X. "Modification Signatory Attorneys General" shall mean the Attorney General, or his or her designee, of each of the following states that have agreed to this modification of the Final Judgment: Arizona, Arkansas, California, Connecticut, Delaware, Florida, Idaho, Illinois, Iowa, Kansas, Kentucky, Maine, Maryland, Massachusetts, Michigan, Mississippi, Montana, Nevada, North Carolina, Ohio, Oregon, Pennsylvania, South Dakota, Tennessee, Texas, Washington, and Wisconsin.

ii. Paragraph Y. "YAZ®" shall mean the oral contraceptive product composed of a combination of drospirenone and ethinyl estradiol approved for marketing by FDA pursuant to NDAs 21-676, 21-873, and 22-045 under the brand name "YAZ®."

b. In addition to the terms contained in the Final Judgment, "Section XI. YAZ® ADVERTISING" is added with the following Paragraphs:

i. Bayer shall disseminate corrective advertising that addresses the issues identified in the Warning Letter. The corrective advertising campaign shall consist of a television advertisement and a print advertisement that have been approved by DDMAC and reviewed

by the Modification Signatory Attorneys General prior to submission of this Joint Motion. The television advertisement shall be broadcast on national cable and network television and the print advertisement shall be published in magazines with national distribution. The specific content and timing of this advertising campaign shall be as specified and approved by DDMAC and reviewed by the Modification Signatory Attorneys General prior to the submission of this Joint Motion. Bayer shall spend at least $20 million on this corrective advertising campaign. Bayer's dissemination of the advertising described in this paragraph shall not be construed as an admission by Bayer that the advertisements identified in the Warning Letter were false, misleading, or deceptive in any manner. Nor shall Bayer's dissemination of the advertising described in this paragraph be considered evidence of any liability, wrongdoing, or fault by Bayer.

ii. Bayer agrees to submit all new Direct to Consumer ("DTC") television advertising campaigns for YAZ® to FDA for pre review, wait until Bayer receives a response from FDA prior to running the advertising campaign, and to modify such advertising consistent with any final written comments received from FDA. Non-material modifications to existing advertising campaigns are not covered by this paragraph.

iii. Bayer shall not run print advertising for YAZ suggesting or marketing YAZ®'s effectiveness at treating selected symptoms of

the FDA-approved indication(s) unless the drug's specific FDA-approved indication(s) is/are stated as clearly and conspicuously in the same promotional spread as the symptoms referenced.

iv. Bayer's obligations with respect to paragraphs ii and iii shall remain in effect for six years following the date this Order Modifying Final Judgment is entered by the court.

v. Bayer shall submit to each Modification Signatory Attorney General on the anniversary of the Effective Date of this Modification a written affirmation setting forth Bayer's compliance with Section XI.

c. In addition to the terms contained in the Final Judgment, "Section XII RELEASE RE YAZ®" is added and with the following paragraphs.

i. Section XII shall pertain to the product YAZ® only and does not alter or modify the release set forth in Section VI of the Final Judgment.

ii. Based upon their investigation into Bayer's promotional and marketing practices regarding YAZ® and whether those practices violate the Final Judgment, the Modification Signatory Attorneys General have concluded that the Final Judgment as modified per this Order Modifying Final Judgment is the appropriate resolution of any alleged violations of the Final Judgment by Bayer regarding its marketing and promotion of the product YAZ® as described by the Warning Letter attached as Exhibit 2 and incorporated by this

reference as though set forth in full.

iii. In Consideration of the terms set forth in Section XI, by execution of this modification of Final Judgment, each Modification Signatory Attorney General, as defined in Section I, Paragraph X, releases and forever discharges, to the fullest extent permitted by law, Bayer and all of its past and present officers, directors, shareholders, employees, affiliates, subsidiaries, predecessors, assigns and successors (hereinafter referred to collectively as the "Released Parties"), from contempt proceedings that were or could have been asserted against the Released Parties by the Modification Signatory Attorneys General for the marketing and promotion of YAZ® by engaging in only the specific conduct described in the Warning Letter attached hereto as Exhibit 2 and incorporated by this reference as though set forth in full.

iv. The Modification Signatory Attorneys General also release and forever discharge, to the fullest extent permitted by law, the Released Parties from any other claims or causes of action under the following consumer protection statutes: ARIZONA - Consumer Fraud Act, A.R.S. § 44-1521, et seq.; ARKANSAS – Deceptive Trade Practices Act, Ark. Code Ann. § 4-88-101 et seq.; CALIFORNIA - Bus. & Prof. Code, §§ 17200 et seq.; CONNECTICUT – Connecticut Unfair Trade Practices Act, Conn. Gen. Stat. § 42- 110 et seq.; DELAWARE - Consumer Fraud Act, 6 Del.C. Section 2511, et seq.; FLORIDA - Deceptive and Unfair

Trade Practices Act, Fla. Stat. Ch. 501.201 et seq.; IDAHO - Consumer Protection Act, Idaho Code § 48-601 et seq.; ILLINOIS - Consumer Fraud and Deceptive Business Practices Act, 815 ILCS § 505/1 et seq.; IOWA - Iowa Consumer Fraud Act, Iowa Code Section 714.16; KANSAS - Consumer Protection Act, K.S.A. 50-623 et seq.; KENTUCKY - Consumer Protection Statute, KRS 367.170; MAINE - Unfair Trade Practices Act, 5 M.R.S.A. § 207 et seq.; MARYLAND - Consumer Protection Act, Md. Code Ann., Com. Law § 13-101 et seq.; MASSACHUSETTS - Consumer Protection Act, M.G.L. c. 93A et seq.; MICHIGAN - Consumer Protection Act, Mich. Comp. Laws § 445.901 et seq.; MISSISSIPPI - Consumer Protection Act, Miss. Code Ann. § 75-24-1 et seq.; MONTANA - Mont. Code Ann. § 30-14-101 et seq.; NEVADA - Deceptive Trade Practices Act, Nevada Revised Statutes 598.0903 et seq.; NORTH CAROLINA - Unfair and Deceptive Trade Practices Act, N.C. Gen. Stat. § 75-1.1 et seq.; OHIO - Consumer Sales Practices Act, R.C. 1345.01 et seq.; OREGON - Unlawful Trade Practices Act, ORS 646.605 to 646.656; PENNSYLVANIA - Unfair Trade Practices and Consumer Protection Law, 73 P.S. § 201-1 et seq.; SOUTH DAKOTA - Deceptive Trade Practices Act, S.D. Codified Laws § 37-24, et seq.; TENNESSEE - Tennessee Consumer Protection Act, Tenn. Code Ann. §§ 47-18-101 et seq.; TEXAS - Deceptive Trade Practices - Consumer Protection Act, Tex. Bus. and Com. Code § 17.47, et seq.; WASHINGTON -

Unfair Business Practices/Consumer Protection Act, R.C.W. 19.86 et seq.; WISCONSIN - Wis. Stat. § 100.18 et seq. (Fraudulent Representations) and Wis. Stat. § 100.182 et seq. (Fraudulent Drug Advertising) that were or could have been asserted against the Released Parties by the Modification Signatory Attorneys General for the marketing and promotion of YAZ® by engaging in only the specific conduct described in the Warning Letter attached hereto as Exhibit 2 and incorporated by this reference as though set forth in full. This release does not extend to conduct or advertisements by the Released Parties that were not specifically described in the Warning Letters attached hereto as Exhibit 2 including, but not limited to, conduct that occurred prior to or subsequent to the described conduct, conduct pertaining to advertisements not addressed in the Warning Letter, or conduct beyond the scope of what is described in the Warning Letter.

d. Notwithstanding any term of this Modification, specifically reserved and excluded from the Released Claims as to any entity or person, including Released Parties, are any and all of the following:

i. Any criminal liability that any person or entity, including Released Parties, has or may have to any or all of the Modification Signatory Attorneys General;

ii. Any civil or administrative liability that any person or entity, including Released Parties, has or may have to any or all of the Modification Signatory Attorneys General, under any statute,

regulation or rule not expressly covered by the release in Paragraph iii. above, including, but not limited to, any and all of the following claims:

1. State or federal antitrust violations;

2. Reporting practices, including "best price", "average wholesale price" or "wholesale acquisition cost";

3. Medicaid violations, including federal Medicaid drug rebate statute violations, Medicaid fraud or abuse, and/or kickback violations related to any State's Medicaid program;

4. State false claims violations; and,

5. Claims to enforce the terms and conditions of this Modification.

iii. Any liability under the above-cited consumer protection laws of any or all of the Modification Signatory Attorneys General which any person or entity, including Released Parties, has or may have to individual consumers of State program payors of said Individual States, and which have not been specifically enumerated as included herein.

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7. Plaintiff and Defendant, signifying by their signatures their approval of both the form of the Modification and the substance of the Modification, thus request this Court to Order the entry of the Modification of the Final Judgment as set forth in Paragraph 6, above.

Dated: Feb 6, 2009

Respectfully Submitted,

EDMUND G. BROWN JR.
Attorney General of California

[redacted]

JUDITH FIORENTINI
Deputy Attorney General
Attorneys for Plaintiff

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Dated: Feb. 2, 2009

Defendant
BAYER CORPORATION

BY: [redacted]
GEORGE J. LYKOS
Chief Legal Officer of Bayer Corporation

Dated: 2.5.09

Sidley Austin LLP

by: [redacted]
Kristin Graham Koehler
Attorney for Defendant Bayer Corporation

Dated: _____

DLA Piper LLP (US)

by: _____
Christopher M. Young
Attorney for Defendant Bayer Corporation

Dated: _____

Defendant
BAYER CORPORATION

BY: _____
GEORGE J. LYKOS
Chief Legal Officer of Bayer Corporation

Dated: _____

Sidley Austin LLP

by: _____
Kristin Graham Koehler
Attorney for Defendant Bayer Corporation

Dated: 2-5-09

DLA Piper LLP (US)

by: [redacted]
Christopher M. Young
Attorney for Defendant Bayer Corporation

ORDER

Good cause appearing therefore, IT IS ORDERED that the Final Judgment entered by this Court on January 23, 2007, is modified to add Paragraphs X and Y to Section I. DEFINITIONS, to add Section XI. YAZ® Advertising, and to add Section XII RELEASE RE YAZ®, as set forth in Paragraph 6 above.

Dated: _____

_____
JUDGE OF THE SUPERIOR COURT

Exhibit 1

FILED
Clerk of the Superior Court
JAN 23 2007
By: M. CHARTER, Deputy

SUPERIOR COURT OF THE STATE OF CALIFORNIA

COUNTY OF SAN DIEGO

THE PEOPLE OF THE STATE OF CALIFORNIA, Plaintiff, v. **BAYER CORPORATION,** Defendants.	Case No. 878812 **FINAL JUDGMENT** Dept: Judge:

A. Plaintiff, the People of the State of California ("the People" or "Plaintiff"), having filed its complaint and appearing through Edmund G. Brown Jr., Attorney General of the State of California, by Albert Norman Shelden, Senior Assistant Attorney General; Sanford Feldman, Supervising Deputy Attorney General; and Judith A. Fiorentini, Deputy Attorney General; and defendant Bayer Corporation ("Bayer") appearing individually and through its attorneys, Sidley Austin LLP by Kristen Graham Koehler, Esq.; DLA Piper by Christopher M. Young, Esq.; and George J. Lykos, Chief Legal Officer of Bayer Corporation, having stipulated that this Final Judgment (hereafter "Judgment") may be signed by any judge of the San Diego County Superior Court; and

B. The People and Bayer ("the parties") having consented to the entry of this Judgment, without this Judgment constituting evidence against or any admission by any party, and without

any trial of any issue of fact or law, and without this Judgment constituting any admission of liability or wrongdoing by Bayer or any other party; and

C. Plaintiff and Bayer acknowledge that, in addition to this Judgment, Bayer has entered into similar settlement agreements with the States and Commonwealths of Arizona, Arkansas, Connecticut, Delaware, Florida, Idaho, Illinois, Iowa, Kansas, Kentucky, Maine, Maryland, Massachusetts, Michigan, Mississippi, Montana, Nevada, North Carolina, Ohio, Oregon, Pennsylvania, South Carolina, South Dakota, Tennessee, Texas, Vermont, Virginia, Washington, and Wisconsin. This Judgment, and the other aforementioned settlement agreements, are referred to collectively as the "Settlement Documents."

The Court having considered the pleadings and the Stipulation for Entry of Final Judgment executed by the Plaintiff and Bayer and filed herewith, and good cause appearing,

IT IS HEREBY ORDERED, ADJUDGED AND DECREED that Judgment may be entered in this matter as follows:

I. DEFINITIONS

The following definitions shall be used in construing this Judgment:

A. "Adverse Events" shall mean an adverse event associated with the use of a drug in humans. "Serious Adverse Events" are those that, at any dose, are fatal, life-threatening, disabling or incapacitating; result in hospitalization; prolong a hospital stay; or are associated with congenital abnormality. In addition, any event not meeting the above criteria may still be deemed Serious if such an event jeopardizes the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

B. "Baycol®" shall mean cerivastatin sodium.

C. "Bayer" shall mean the Bayer Corporation and its U.S.-based affiliates, subsidiaries, predecessors, successors, and assigns.

D. "Bayer Website" shall mean Bayer's main Internet site, currently http://www.pharma.bayer.com, or a link from that site.

E. "Bayer-Sponsored" shall mean Bayer is responsible for regulatory approvals, site selection, protocol development, initiation, monitoring, safety reporting, and Data analysis, even

if some or all of these activities are transferred to another party (e.g., Clinical Research Organization). A Clinical Study is not "Bayer-Sponsored" if it is initiated by a third party for which Bayer provides some support, for example by way of a grant or supply of medication, but with sponsor responsibilities for study initiation and management agreed in writing to reside with the third party. For purposes of this Judgment only, studies conducted by Bayer's parent entity and its foreign affiliates shall be considered Bayer-Sponsored.

F. "Clinical Study" shall mean any research project that prospectively assigns human subjects to intervention and concurrent comparison/control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. The term "Clinical Study" is not limited to a research study that is randomized or blinded; and is not limited to studies conducted in the United States.

G. "Clinical Study Report" shall mean a description of the Protocol, a summary of all the Data, a description and the results of statistical analyses of the Data, a listing of the common Adverse Events and a more detailed listing of the Serious Adverse Events, and the clinically relevant conclusions drawn from the Data in a Bayer-Sponsored Clinical Study, including the answers to the questions posed in the Protocol.

H. "Compliance Provisions" shall mean Paragraphs 6 through 16 of this Judgment.

I. "Covered Conduct" shall mean Bayer's promotional and marketing practices regarding the prescription drug Baycol®.

J. "Data" shall mean all of the results and outcome measurements obtained from a Clinical Study.

K. "Effective Date" shall mean the date by which all Parties have executed the Judgment.

L. "Exploratory Phase II Clinical Study" shall mean a study with less than fifty (50) participants and where a health outcome is not a predefined endpoint of the study.

M. "Individual State" and "State" shall mean each Signatory Attorney General who is participating in the Multistate Working Group.

N. "Multistate Working Group" ("MSWG") shall mean the Attorneys General and their staffs representing the States and Commonwealths of Arizona, Arkansas, California,

Connecticut, Delaware, Florida, Idaho, Illinois, Iowa, Kansas, Kentucky, Maine, Maryland, Massachusetts, Michigan, Mississippi, Montana, Nevada, North Carolina, Ohio, Oregon, Pennsylvania, South Carolina, South Dakota, Tennessee, Texas, Vermont, Virginia, Washington, and Wisconsin.

O. "Non-Exploratory Phase II Clinical Study" shall mean a study with fifty (50) or more participants or where a health outcome is a pre-defined endpoint of the study.

P. "Parties" shall mean Bayer and the Individual States.

Q. "Post" information shall mean to provide access to the information on an Internet site that provides no-cost and unrestricted access to both the site and the information Bayer has provided through the site. The Posting obligations exclusively reside with Bayer as defined in paragraph C, not Bayer's parent entity or its foreign affiliates. Bayer does not fulfill a requirement to Post information under this Judgment if it does so on an Internet site, other than the Bayer Website, that contains any advertisement by any pharmaceutical company or for any pharmaceutical product.

R. "Products" shall mean any pharmaceutical or biological product manufactured, distributed, sold, marketed or promoted in any way by Bayer, solely or in conjunction with other companies in the United States.

S. "Protocol" shall mean the investigational plan that is used to conduct the Clinical Study. The Protocol for an acute phase of a Clinical Study is separate from the Protocol of a continuation or extension phase of a Clinical Study.

T. "Signatory Attorney General" shall mean the Attorney General, or his or her designee, of each state in the Multistate Working Group investigating Bayer's promotion and marketing practices regarding Baycol.®

U. "State Consumer Protection Laws" shall mean the consumer protection laws under which the Signatory Attorneys General have conducted their investigation.[2]

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2 ARIZONA Consumer Fraud Act, Ariz. Rev. Stat. §44-1521, *et. seq.*]; ARKANSAS - Deceptive Trade Practices Act, Ark. Code Ann. § 4-88-101 *et seq.*; CALIFORNIA Business and Professions Code § 17200 *et seq*; CONNECTICUT – Connecticut Unfair Trade Practices Act,

V. "Subject Matter of this Judgment" shall mean the Signatory Attorneys' General investigation under the State Consumer Protection Laws of Bayer's promotional and marketing practices regarding the prescription drug Baycol®.

W. "Study Completion Date" shall mean the date on which the last observation is made either of the last patient who remains enrolled in the Clinical Study or following a decision to terminate the Clinical Study early, whichever happens first.

II. JURISDICTION

1. The Court has jurisdiction over the subject matter of this action.

2. The Court has jurisdiction over the parties to this action.

3. Venue is proper in this Court.

4. The complaint states a cause of action against Defendant Bayer under Section 17200 of the California Business and Professions Code.

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Conn. Gen. Stat. §42-110 *et seq.*; DELAWARE - Consumer Fraud Act, 6 Del.C. Section 2511, *et seq.*, UDTPA, 6 Del.C. Section 2531, *et seq.*; FLORIDA - Deceptive and Unfair Trade Practices Act, Fla. Stat. Ch. 501.201 *et seq.*; IDAHO - Consumer Protection Act, Idaho Code § 48-601 *et seq.*; ILLINOIS - Consumer Fraud and Deceptive Business Practices Act, 815 ILCS § 505/1 *et seq.* (2002); IOWA - Iowa Consumer Fraud Act, Iowa Code Section 714.16; KANSAS – Kansas Consumer Protection Act, K.S.A. 50-623, *et seq.*; KENTUCKY - Consumer Protection Statute, KRS 367.170; MAINE – Unfair Trade Practices Act, 5 M.R.S.A. section 205-A *et.* seq; MARYLAND - Consumer Protection Act, Maryland Commercial Law Code Annotated § 13-101 *et seq.*; MASSACHUSETTS - Consumer Protection Act, M.G.L. c. 93A *et seq.*; MICHIGAN - Consumer Protection Act, Mich. Comp. Laws §445.901 *et seq.* (2004); MISSISSIPPI - Consumer Protection Act, Miss. Code Ann. § 75-24-1 *et seq.*; MONTANA - Mont. Code Ann. § 30-14-101 *et seq.*; NEVADA - Deceptive Trade Practices Act, Nevada Revised Statutes 598.0903 *et seq.*; NORTH CAROLINA - Unfair and Deceptive Trade Practices Act, N.C.G.S. § 75-1.1 *et seq.*; OHIO - Consumer Sales Practices Act, R.C. § 1345.01 *et seq.*; OREGON - Unlawful Trade Practices Act, ORS 646.605 to 646.656; PENNSYLVANIA - Unfair Trade Practices and Consumer Protection Law, 73 P.S. § 201-1 *et seq.*; SOUTH CAROLINA - Unfair Trade Practices Act, Sections 39-5-10 *et seq.*; SOUTH DAKOTA – Deceptive Trade Practices and Consumer Protection Law, SDCL Chapter 37-24; TENNESSEE - Consumer Protection Act, Tenn. Code Ann. § 47-18-101 *et seq.*, (1977); TEXAS - Deceptive Trade Practices and Consumer Protection Act, Tex. Bus. And Com. Code § 17.41 *et seq.*, (Vernon 2002); VERMONT - Consumer Fraud Act, 9 V.S.A. § 2451 *et seq.*; VIRGINIA - Virginia Consumer Protection Act, 59.1 -196 *et seq.*; WASHINGTON - Washington Consumer Protection Act – R.C.W. 1986 *et seq*; WISCONSIN - Wis. Stat. § 100.18 (Fraudulent Representations).

5. The Judgment is entered based upon the background information described in Paragraph 2 of the Stipulation for Entry of Final Judgment.

III. COMPLIANCE PROVISIONS

6. Pursuant to Sections 17203 of the California Business and Professions Code, Bayer shall comply with all applicable laws and regulations relating to the marketing, sale and promotion of its Products. Bayer shall not make any false, misleading or deceptive representation regarding any of its Products in violation of any applicable laws and regulations including, but not limited to, California Business and Professions Code Section 17200.

7. Any terms that are not defined above in Section I shall be interpreted to have the same meaning as they have in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines for Industry: Structure and Content of Clinical Study Reports (July 1996), which is annexed as Exhibit 1.

8. Bayer shall register all Non-Exploratory Phase II, and all Phase III and IV Bayer-Sponsored Clinical Studies on ClinicalTrials.gov in accordance with the following requirements:

a. Bayer shall register Non-Exploratory Phase II, and all Phase III and IV Bayer-Sponsored Clinical Studies on ClinicalTrials.gov at the time such studies are initiated.

b. At the time of registration of a Non-Exploratory Phase II Bayer-Sponsored Clinical Study, Bayer will post 15 of the 20 data set items established by the World Health Organization ("WHO"), attached as Exhibit 2, to ClinicalTrials.gov (that is, all data set items except 10, 13, 17, 19 and 20) and, if there is a change in status, update data set 18 in a timely manner. Bayer will populate the remaining five WHO data fields either when the Product reaches Phase III (and a Phase III Bayer-Sponsored Clinical Study is initiated), or when the Summary of the Clinical Study Report is Posted, whichever occurs first. In the event that a Non-Exploratory Phase II Bayer-Sponsored Clinical Study of a Bayer Product that is approved for marketing and is commercially available in the United States is terminated prior to one or more of its endpoints, Bayer will populate the remaining five WHO data fields no later than 30 days following termination of the study.

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c. At the time of registration of a Phase III or IV Bayer-Sponsored Clinical Study, Bayer will post all 20 data set items to ClinicalTrials.gov.

9. Bayer shall Post on ClinicalStudyResults.org Summaries of Clinical Study Reports ("Summaries of Clinical Study Reports") for all Phase II, III and IV Bayer-Sponsored Clinical Studies of Bayer Products that are approved for marketing and are commercially available in the United States. Should a publicly funded website for such postings become available after the Date of this Judgment, Bayer shall also Post on that website as well. Such summaries shall conform to ICH E3 principles and to the template published in the Federal Register, Vol. 61, July 17, 1996, Page 37320 *et seq.*

10. For studies initiated after the date of this Judgment, Bayer will also make all reasonable efforts to encourage the publication of, or in the alternative, secure the right to Post, Summaries of Clinical Study Reports in which Bayer had significant participation but did not sponsor.

11. The Summaries of Clinical Study Reports that Bayer Posts shall accurately reflect the methodology used to conduct the Clinical Study and summaries of the Data obtained during the Clinical Study. The Summaries of Clinical Study Reports that Bayer Posts shall include not only the generic and brand names of the Bayer Products, but also a listing of all aliases under which the Bayer Products may be known at the time of Posting, including the serial numbers, code names and chemical descriptions.

12. Bayer shall Post the Summaries of Clinical Study Reports in accordance with the following time requirements:

a. With respect to Products approved for marketing and commercially available in the United States for any indication prior to the Date of this Judgment

(i) Studies completed prior to the Date of this Judgment: Summaries of Phase II, III and IV Clinical Study Reports and summaries of any other studies material to a physician's judgment in relation to prescribing Products in the United States, with a Study Completion Date that occurred between July 1, 2005, and the Date of this Judgment will be posted within 120 days of the Effective Date of this Judgment or within twelve months of the Study Completion Date, whichever is later.

(ii) Studies completed after the Date of Judgment: Summaries of Clinical Study Reports for Phase II, III and IV Clinical Studies and summaries of any other studies material to a physician's judgment in relation to prescribing Products in the United States, completed after the Date of this Judgment will be Posted within twelve months of the Study Completion Date.

b. With respect to Products approved for marketing and commercially available in the United States for an initial indication after the Date of this Judgment, Summaries of Clinical Study Reports and summaries of any other studies material to a physician's judgment in relation to prescribing Products in the United States will be posted within twelve months of the Study Completion Date or first marketing, whichever is later.

c. The parties recognize that, in some instances, there may be a delay in Posting complete Summaries of Clinical Study Reports because Bayer must seek intellectual-property protection or comply with policies of Peer Reviewed Journals to which manuscripts have been submitted for publication; and, further, that Bayer may be required to withhold certain Summaries of Clinical Study Reports to comply with confidentiality provisions in agreements with other parties.

d. In regard to confidentiality agreements, in all future Clinical Studies Bayer will use reasonable efforts to exclude provisions limiting the publication of Summaries of Clinical Study Reports. For all past Clinical Studies with such confidentiality agreements, Bayer will make reasonable efforts to secure the right to Post the Summaries of Clinical Study Reports.

e. The Signatory Attorneys General and Bayer do not intend Bayer's determination of materiality for posting to be admissible in private litigation or to constitute an admission by Bayer that the information posted is in fact material to prescribing decisions.

13. Bayer shall clearly and conspicuously state on the Home Page of the Bayer Website that the Posted information is available at ClinicalTrials.gov and ClinicalStudyResults.org. and shall prominently feature links to those websites on the Home Page of the Bayer Website.

14. Within two weeks of the Date of this Judgment, Bayer shall arrange and pay for the publication of the advertisement annexed hereto as Appendix 3 to run in the next available print and electronic editions (for at least one month on the electronic editions) of each of the following journals: Journal of the American Medical Association, New England Journal of Medicine, Annals of Internal Medicine, Journal of the American Board of Family Practice, Pharmacotherapy, Annals of Pharmacotherapy, and the Journal of Clinical Pharmacology & Therapeutics. Bayer shall arrange and pay for each of the advertisements to be placed between the front cover and the first article in each journal. Letters to the editor do not constitute articles for the purpose of this paragraph. Each advertisement must be at least one-half page in size.

15. Nothing in this Judgment shall require Bayer to:

a. Take an action that is prohibited by the federal Food, Drug and Cosmetic Act ("FDCA") or any regulation promulgated thereunder, or by the Food and Drug Administration ("FDA"); or

b. Fail to take an action that is required by the FDCA or any regulation promulgated thereunder, or by FDA. Any written or oral promotional claim subject to this Judgment which is the same or substantially the same as the language prescribed by FDA shall not constitute a violation of this Judgment.

16. Bayer shall:

a. Provide a copy of the Compliance Provisions of this Judgment to all current employees having direct responsibility for Posting Clinical Study information; and will make this Judgment accessible on Bayer's intranet site to all current employees having responsibility for marketing and promoting its Products ("Relevant Persons");

b. Obtain certifications from the Relevant Persons that they have received and/or reviewed a copy of the Compliance Provisions of this Judgment, have read them, understand their responsibilities and duties in accordance therewith, and will abide by the Compliance Provisions; and

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c. Submit to each Signatory Attorney General, on the anniversary of the Effective Date of this Judgment, a written affirmation setting forth Bayer's compliance with this paragraph.

IV. DISBURSEMENT OF PAYMENTS: PAYMENT TO THE STATES

17. Within thirty (30) days of the Effective Date of this Judgment, Bayer shall pay $8,000,000.00 to the States by electronic fund transfer made payable to the Oregon Attorney General's Office which shall divide and distribute these funds as designated by and in the sole discretion of the Signatory Attorneys General as part of the consideration for the termination of their respective investigations under the State Consumer Protection Laws regarding the Subject Matter of this Judgment. Said payment shall be used by the States as and for attorneys' fees and other costs of investigation and litigation, or to be placed in, or applied to, the consumer protection enforcement fund, consumer education, litigation or local consumer aid fund or revolving fund, used to defray the costs of the inquiry leading hereto, or for other uses permitted by state law, at the sole discretion of each Signatory Attorney General.[3]

V. GENERAL PROVISIONS

18. This Judgment shall be governed by the laws of California.

19. This Judgment may be executed in counterparts, and by different signatories on separate counterparts, each of which shall be deemed to constitute an original counterpart hereof, and all of which shall together constitute one and the same Judgment. One or more counterparts of this Judgment may be delivered by facsimile or electronic transmission with the intent that it or they shall constitute an original counterpart hereof.

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3 For ARKANSAS, the money shall be placed in the Arkansas Attorney General's Consumer Education and Enforcement Fund and held in trust for purposes directly related to Arkansas consumer protection efforts. For CALIFORNIA payment will go to the California Unfair Competition Fund; DELAWARE'S payment will go to the Consumer Protection Fund. In MASSACHUSETTS, the money shall be deposited into the Local Consumer Aid Fund pursuant to M.G.L. c. 12, section 11G. In OREGON, the money shall be deposited to the Consumer Protection and Education Revolving Account established pursuant to ORS 180.095. In PENNSYLVANIA, funds distributed to the Pennsylvania Office of Attorney General may be used for costs of investigation, attorney fees and for future consumer protection and public protection purposes. For WASHINGTON state, in lieu of direct restitution, the funds may be used for recovery of costs and fees and consumer education cy pres.

20. This Judgment shall not be construed or used as a waiver or any limitation of any defense otherwise available to Bayer. This Judgment is made without trial or adjudication of any issue of fact or law or finding of liability of any kind. Nothing in this Judgment, including this paragraph, shall be construed to limit or to restrict Bayer's right to use this Judgment to assert and maintain the defenses of res judicata, collateral estoppel, payment, compromise and settlement, accord and satisfaction, or any other legal or equitable defenses in any pending or future legal or administrative action or proceeding.

21. This Judgment shall become effective on the Effective Date and Bayer's obligations to Post information and otherwise publish its Clinical Study Reports shall remain in effect for Ten (10) years following the Effective Date.

VI. RELEASE

22. Based upon their investigation into Bayer 's promotional and marketing practices regarding Baycol, the Signatory Attorneys General have concluded that this Judgment is the appropriate resolution of any alleged violations of the State Consumer Protection Laws. The Signatory Attorneys General acknowledge by their execution hereof that this Judgment terminates their investigation under the State Consumer Protection Laws into Bayer's promotional practices regarding Baycol® prior to the Effective Date of this Judgment.

23. In consideration of the Compliance Provisions, payments, undertakings and acknowledgments provided for in this Judgment, and conditioned upon Bayer's full payment of the amount specified in Paragraph 17 and subject to the reservations set forth in Paragraph 24 by its execution of this Judgment, each Signatory Attorney General, as defined in Section I, Paragraph T, releases and forever discharges, to the fullest extent permitted by law, Bayer and all of its past and present officers, directors, shareholders, employees, affiliates, subsidiaries, predecessors, assigns and successors (hereinafter referred to collectively as the "Released Parties"), from the following: all civil claims, causes of action, counterclaims, setoffs, demands, actions, suits, rights, liabilities, damages, restitution, fines, costs and penalties under the above-cited statutes arising from the Covered Conduct, also defined as the Subject Matter of this Judgment in Section I, Paragraph V, as described in Paragraph 2 of the Stipulation

for Entry of Final Judgment, that were or could have been asserted against the Released Parties by the Signatory Attorneys General on or after February 18, 1998. This release does not apply to any conduct occurring after the Effective Date of this Judgment.

24. Notwithstanding any term of this Judgment, specifically reserved and excluded from the Released Claims as to any entity or person, including Released Parties, are any and all of the following:

a. Any criminal liability that any person or entity, including Released Parties, has or may have to any or all of the Signatory Attorneys General;

b. Any civil or administrative liability that any person or entity, including Released Parties, has or may have to any or all of the Signatory Attorneys General, under any statute, regulation or rule not expressly covered by the release in Paragraph 23 above, including, but not limited to, any and all of the following claims:

(i) State or federal antitrust violations;

(ii) Reporting practices, including "best price", "average wholesale price" or "wholesale acquisition cost";

(iii) Medicaid violations, including federal Medicaid drug rebate statute violations, Medicaid fraud or abuse, and/or kickback violations related to any State's Medicaid program;

(iv) State false claims violations; and,

(v) Claims to enforce the terms and conditions of this Judgment.

c. Any liability under the above-cited consumer protection laws of any or all of the Signatory Attorneys General which any person or entity, including Released Parties, has or may have to individual consumers or State program payors of said Individual States, and which have not been specifically enumerated as included herein.

VII. DISPUTES REGARDING COMPLIANCE

25. For the purposes of resolving disputes with respect to compliance with this Judgment, should any of the Signatory Attorneys General have cause to believe that Bayer has violated a provision of this Judgment subsequent to the Effective Date of this Judgment, then such Attorney

General shall notify Bayer in writing of the specific objection, identify with particularity the provisions of this Judgment and/or the State Consumer Protection Law that the practice appears to violate, and give Bayer thirty (30) business days to respond to the notification; provided, however, that a Signatory Attorney General may take any action where the Signatory Attorney General concludes that, because of the specific practice, a threat to the health or safety of the public requires immediate action.

26. Upon giving Bayer thirty (30) business days to respond to the notification described in Paragraph 25 above, the Signatory Attorney General shall be permitted to serve a document request for relevant, non-privileged, non-work-product records and documents in the possession, custody or control of Bayer that relate to Bayer's compliance with each provision of this Judgment as to which legally sufficient cause has been shown. In response to that document request, Bayer will make responsive documents available to the Signatory Attorneys General.

VIII. PENALTIES FOR FAILURE TO COMPLY

27. The State may assert any claim that Bayer has violated this Judgment in a separate civil action to enforce this Judgment, or to seek any other relief afforded by law. In any such action or proceeding, relevant evidence of conduct that occurred before the Effective Date shall be admissible on any material issue, including alleged willfulness, intent, knowledge, contempt or breach, to the extent permitted by law. Bayer does not waive any objection it may have to the admissibility of any such evidence, as permitted by law.

IX. COMPLIANCE WITH ALL LAWS

28. Except as expressly provided in this Judgment, nothing in this Judgment shall be construed as:

a. Relieving Bayer of its obligation to comply with all applicable state laws, regulations or rules, or granting permission to engage in any acts or practices prohibited by such law, regulation or rule; or

b. Limiting or expanding in any way any right the State may otherwise have to obtain information, documents or testimony from Bayer pursuant to any applicable state law, regulation or rule, or any right Bayer may otherwise have to oppose any subpoena, civil

investigative demand, motion, or other procedure issued, served, filed, or otherwise employed by the State pursuant to any such state law, regulation, or rule.

X. NOTICES UNDER THIS JUDGMENT

29. Any notices that must be sent to the State or to Bayer under this Judgment shall be sent by overnight United States mail. The documents shall be sent to the following addresses:

For the MS WG:

Suzanne D. Sonneborn
Assistant Attorney General, Consumer Protection Division
G Mennen Williams Building, 6th Floor
525 West Ottawa Street
Post Office Box 3021 3
Lansing, Michigan 48909
Telephone: 517-335-0855
Facsimile: 5 17-335-1935

David Anthony Hart
Assistant Attorney General
1 162 Court Street NE
Salem, Oregon 97301 -4096
Telephone: 503-947-4333
Facsimile: 503-378-501 7

For Bayer:

Kristin Graham Koehler, Esquire
Sidley Austin LLP
1501 K Street, N.W.
Washington, D.C. 20005
Telephone: 202-736-8359
Facsimile: 202-736-8711

and

Chief Legal Officer
Bayer Corporation
100 Bayer Road
Pittsburgh, PA 15205
Telephone: 412-777-5774
Facsimile: 412-777-4417

30. The Clerk is ordered to enter this Judgment forthwith.

Date: Jan 23, 2002.

[redacted]
JUDGE OF THE SUPERIOR COURT

Exhibit 2

3697.2

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Reinhard Franzen
President & Chief Executive Officer
Bayer HealthCare Pharmaceuticals, Inc.
P.O. Box 1000
Montville, NJ 07045-1000

Re: NDA # 21-676, 21-873, 22-045
YAZ® (drospirenone and ethinyl estradiol) Tablets
MACMIS ID# 16473

WARNING LETTER

Dear Mr. Franzen:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed two 60-second direct-to-consumer (DTC) broadcast television advertisements (TV Ads) entitled "Not Gonna Take it" (ZYRA-6323) and "Balloons" (ZYRA-6567) for YAZ® (drospirenone and ethinyl estradiol) Tablets (YAZ) submitted by Bayer HealthCare Pharmaceuticals, Inc. (Bayer) under cover of separate Forms FDA-2253. The TV Ads are misleading because they broaden the drug's indication, overstate the efficacy of YAZ, and minimize serious risks associated with the use of the drug. Thus, the TV Ads misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(n), 352(f)(1) & 321(n), and FDA's implementing regulations. 21 CFR 201.100(c)(1); 201.128; 202.1(e)(5)(iii) & (e)(6)(i). These violations are concerning from a public health perspective because they encourage use of YAZ in circumstances other than those in which the drug has been approved, over-promise the benefits and minimize the risks associated with YAZ.

Background

According to the INDICATIONS AND USAGE section from the FDA-approved product labeling (PI), YAZ is approved for the following indications (in pertinent part):

> [F]or the prevention of pregnancy in women who elect to use an oral contraceptive. . . .
>
> [F]or the treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception. The effectiveness of YAZ for PMDD when used for more than three menstrual cycles has not been evaluated.

> The essential features of PMDD according to the Diagnostic and Statistical Manual-4th edition (DSM-IV) include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating and weight gain. In this disorder, these symptoms occur regularly during the luteal phase and remit within a few days following onset of menses; the disturbance markedly interferes with work or school, or with usual social activities and relationships with others. Diagnosis is made by healthcare providers according to DSM-IV criteria, with symptomatology assessed prospectively over at least two menstrual cycles. In making the diagnosis, care should be taken to rule out other cyclical mood disorders.
>
> **YAZ has not been evaluated for the treatment of premenstrual syndrome (PMS)** [emphasis added].
>
> [F]or the treatment of moderate acne vulgaris in women at least 14 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche. YAZ should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control.

Additionally, the BRIEF SUMMARY PATIENT PACKAGE INSERT and DETAILED PATIENT PACKAGE INSERT state that:

> . . . YAZ has not been shown to be effective for the treatment of premenstrual syndrome (PMS), a less serious cluster of symptoms occurring before menstruation. If you or your healthcare provider believes you have PMS, you should only take YAZ if you want to prevent pregnancy; and not for the treatment of PMS. . . .

The PI for YAZ includes a BOXED WARNING that states (in pertinent part):

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

Additionally, there are numerous warnings associated with the use of YAZ including, but not limited to, venous and arterial thrombotic and thromboembolic events (such as myocardial infarction, thromboembolism, stroke), hepatic neoplasia, gallbladder disease, and hypertension.

Moreover, YAZ has additional risks because it contains the progestin, drospirenone. Drospirenone has antimineralocorticoid properties which can lead to hyperkalemia in high risk patients, which may result in potentially serious heart and health problems. Women taking YAZ must be concerned about the drug interactions that could increase potassium, in addition to the drug interactions common to all combination oral contraceptives. This additional risk is described in the bolded WARNINGS section of YAZ's PI.

Broadening of Indication

Premenstrual Dysphoric Disorder (PMDD)

"Not Gonna Take It" (ZYRA-6323) & "Balloons" (ZYRA-6567)

The TV Ads misleadingly suggest that YAZ is effective in a broader range of patients and conditions than has been demonstrated by substantial evidence or substantial clinical experience. Specifically, given the overlap in certain symptoms between premenstrual syndrome (PMS) and PMDD, and the material limitation on YAZ's PMDD indication (that it has not been evaluated for the treatment of the less serious condition, PMS), the TV Ads misleadingly suggest that YAZ is appropriate for treating women with PMS, who may not be appropriate candidates for this drug. We note that despite listing certain symptoms of PMDD, nowhere do the TV Ads use the full phrase "premenstrual dysphoric disorder," to more completely distinguish PMDD from PMS, thereby increasing the likelihood that a viewer, in light of the claims and presentations described below, will understand it to be the same as, or substantially similar to, PMS.

The TV Ad "Not Gonna Take It" starts by stating:

- "We all know that birth control pills are 99% effective and can give you shorter, lighter periods. But did you know there's a Pill that could do more?"

It then displays images of energetic, euphoric, playful women singing "We're Not Gonna Take It" as they kick, punch, and push words describing symptoms such as "IRRITABILITY," "MOODINESS," "BLOATING," and "FEELING ANXIOUS," away from the screen, followed by the claim "It's YAZ! And there's no other birth control like it." The screen then displays a listing of symptoms including: irritability; increased appetite; moodiness; fatigue; feeling anxious; headaches; bloating; and muscle aches.

Similarly, the TV Ad "Balloons" starts by stating:

- "All birth control pills are 99% effective and can give you shorter, lighter periods. But there's one Pill that goes beyond the rest. It's YAZ."

It then displays numerous balloons throughout the ad with symptoms, such as, "IRRITABILITY," "MOODINESS," "FEELING ANXIOUS," "BLOATING," "FATIGUE," "MUSCLE ACHES," "HEADACHES," "INCREASED APPETITE," and "ACNE."

The symptoms displayed in these ads are commonly seen in women with PMS, which is a less serious and more common condition than PMDD. PMDD is a disorder whose hallmarks

include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features of PMDD include decreased interest in usual activities, difficulties concentrating, lack of energy, change in appetite or sleep, and feeling out of control. As discussed in the PI, for a diagnosis of PMDD:

> ...the disturbance markedly interferes with work or school, or with usual social activities and relationships with others. Diagnosis is made by healthcare providers according to the DSM-IV criteria, with symptomatology assessed prospectively over at least two menstrual cycles. In making the diagnosis, care should be taken to rule out other cyclical mood disorders.

The TV Ads entirely omit the material limitation from the PI of the drug's PMDD indication – i.e., that "YAZ has not been evaluated for the treatment of premenstrual syndrome (PMS)" – and fail to convey that the drug is only indicated for women who experience the symptoms presented to such a degree that they have PMDD, rather than PMS. As a result of the failure to convey these material facts, and the failure to explain what PMDD is, in contrast to PMS, the TV Ads misleadingly suggest that YAZ is approved to treat women with any severity of the symptoms presented, regardless of whether their symptoms are actually severe enough to constitute PMDD.

We note that the list of symptoms displayed in the TV Ads are accompanied by the text "YAZ treats PMDD" along with a SUPER reading "PMDD is a mood disorder related to the menstrual cycle." However, these disclosures do not suffice to communicate the material fact that YAZ is not approved for treatment of PMS or to overcome the implication created by the totality of the visuals and images in the ads that YAZ is appropriate for any woman who experiences the symptoms presented. We also note that the voiceover states that "YAZ is the only birth control pill proven to treat the emotional and physical premenstrual symptoms that are severe enough to impact your life." However, this claim also fails to communicate that YAZ is not approved for treatment of PMS, and fails to distinguish between PMS and PMDD.

The totality of the visual and audio presentations in both TV ads suggest that YAZ is approved to treat women with any severity of the symptoms presented, including women with PMS, when this is not the case. Thus, the TV Ads misleadingly broaden the indication of the drug.

Acne

In addition, the TV Ads suggest that YAZ is approved for acne of all severities when this is not the case. Specifically, in "Not Gonna Take it," the word "ACNE" appears in large print in the middle of the screen along with the audio claim "It can also help keep your skin clear," which is accompanied by a close-up visual of a woman with completely clear skin. Similarly, in "Balloons," the "ACNE" balloon is prominently displayed on the screen, as it floats by a smiling woman with obviously clear skin, along with the audio claim that YAZ "...also helps keep skin clear." These presentations fail to adequately convey that, as noted in the PI, "YAZ is indicated for the treatment of moderate acne vulgaris..." (emphasis added). While the TV Ads do include a SUPER which refers to "improvement in ... moderate acne" in small,

unbolded print, this does not mitigate the misleading impression created by the prominent audio and visual claims in the TV Ads that YAZ is indicated for acne of all severities.

Overstatement of Efficacy

PMDD

"Balloons" (ZYRA-6567)

The TV Ad is misleading because it suggests that YAZ is more effective than has been demonstrated by substantial evidence or substantial clinical experience. The totality of the audio and visual claims and presentations misleadingly suggests that treatment with YAZ will allow women to say "good-bye" to their symptoms completely. For example, the TV Ad's theme song "Good-Bye to you" plays in the background as energetic, euphoric, playful women release balloons into the air displaying certain symptoms (e.g., irritability, moodiness, feeling anxious, bloating, fatigue, muscle aches, headaches, increased appetite, and acne). The balloons then float up and away from the women misleadingly suggesting that these women are saying, "goodbye" to their symptoms and are now symptom-free, when such an elimination of symptoms has not been demonstrated by substantial evidence or substantial clinical experience. According to the PI, in the primary clinical trial that served as the basis for approval of YAZ in the PMDD population, "...the average decrease (improvement) from baseline was 37.5 points in women taking YAZ, compared to 30.0 points in women taking placebo" (added emphasis). These results do not support the implication that YAZ will result in a complete cessation of PMDD symptoms.

Acne

"Not Gonna Take It" (ZYRA-6323) & "Balloons" (ZYRA-6567)

The TV Ads include close-up images of women with completely clear, acne-free skin. In the TV Ad "Not Gonna Take It," there is an image of a woman with the word "ACNE" prominently displayed on the screen before the word "ACNE" fades away from view. The woman turns her face to the side showing viewers that she has no visible signs of acne on her face, in conjunction with the audio claim "It can also help keep your skin clear." In "Balloons," a woman with obviously clear skin smiles and acknowledges the "ACNE" balloon as it floats away from the center of the screen and disappears into the sky, in conjunction with, the background song "Good-bye to you" and the audio claim that YAZ "...also helps keep skin clear." The overwhelming impression conveyed by the TV Ads is that treatment with YAZ results in clear, acne-free skin for those women suffering from acne when this has not been demonstrated by substantial evidence or substantial clinical experience. As illustrated by Table III in the PI, the percentage of subjects assessed by the Investigator's Static Global Assessment (ISGA) with a 'clear' or 'almost clear' rating at day 15 of cycle 6 was 15% and 21% for subjects receiving YAZ versus 4% and 9% of placebo subjects in Studies 1 and 2, respectively. Furthermore, the mean percent reduction of total lesions at day 15 of cycle 6 was 42% and 46% for subjects receiving YAZ versus 25% and 31% of placebo subjects in studies 1 and 2, respectively. Although these results are significant, they do not demonstrate that YAZ results in clear, acne-free skin for a typical woman; rather, these results demonstrate that it reduces the amount of acne lesions more than placebo but does not

result in completely clear skin for these women. Thus, the TV Ads misleadingly overstate the efficacy of the drug.

Minimization of Risk

"Not Gonna Take It" (ZYRA-6323) & "Balloons" (ZYRA-6567)

The audio communication of serious risk disclosures during the "major statement" is minimized by distracting visuals, numerous scene changes, and other competing modalities such as the background music which combine to interfere with the presentation of the risk information. In "Not Gonna Take It", the fast-paced visuals depict various women looking at pictures, trying on clothes, chatting at a cafe, stretching/exercising in a park, and walking down the street while the audio component describes the major risks associated with YAZ. Similarly, in "Balloons," the background music plays as fast-paced visuals depict various women running in a park, sitting on a scenic waterfront, smiling, walking out of a coffee shop, driving and singing, walking out on a balcony, using an elevator, walking through the street to join friends, in addition, to a pigeon on a building ledge and balloons being released and floating away. These complex presentations distract from and make it difficult for viewers to process and comprehend the important risks being conveyed. This is particularly troubling as some of the risks being conveyed are serious, even life-threatening. The overall effect of the distracting visuals, graphics, concurrent supers and background music is to undermine the communication of important risk information, minimizing these risks and misleadingly suggesting that YAZ is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Conclusion and Requested Action

For the reasons discussed above, the promotional piece misbrands YAZ in violation of the Act, 21 U.S.C. 352(n), 352(f)(1), & 321(n), and FDA implementing regulations. 21 CFR 201.100(c)(1); 201.128; 202.1(e)(5)(iii) & 202.1(e)(6)(i).

DDMAC asks Bayer to immediately cease dissemination of violative promotional materials for YAZ that are the same as or similar to those described above. Please submit a written response to this letter on or before October 20, 2008, describing your intent to comply with this request, listing all promotional materials for YAZ that are the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at (301) 847-8444. In all future correspondence regarding this matter, please refer to MACMIS ID # 16473 in addition to the NDA number(s). If you choose to revise your promotional materials, DDMAC is willing to assist you with your revised materials by commenting on your revisions before you use them in promotion. 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 YAZ comply with each applicable requirement of the Act and FDA implementing regulations. Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas Abrams, R.Ph., M.B.A.
Director
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/

Thomas Abrams
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