CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-683

CORRESPONDENCE

APR - 3 1996

NDA 20-683

Wyeth-Ayerst Laboratories
Attention: Mr. Douglas W. Bitz
P.O. Box 8299
PHILADELPHIA PA 19101

Dear Mr. Bitz:

We have received your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Alesse [levonorgestrel (100 mg)/ethinyl estradiol (20 mg) tablets

Therapeutic Classification: Standard

Date of Application: March 27, 1996

Date of Receipt: March 27, 1996

Our Reference Number: 20-683

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 26, 1996, in accordance with 21 CFR 314.101(a).

If you have any questions concerning this NDA, please contact:

Christina Kish
Consumer Safety Officer
Telephone: (301) 443-3520

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Enid Galliers 4/1/96

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-683
HFD-510/Div. Files
HFD-80
HFD-510/CKish/April 1, 1996/n20683.ak
concurrence: EGalliers 4.1.96

ACKNOWLEDGEMENT (AC)

Memo to the File concerning NDA 20-683

Name of Drug: Alesse

Sponsor: Wyeth-Ayerst

Clinical Use: Oral contraceptive

Dosage and Route of Administration: 20 mcg ethinyl estradiol(EE) and 100 mcg levonorgestrel(LN)--Orally

Comment:
This memo is meant to address the issue of a [redacted]% overage which was used in the clinical trials. This overage of [redacted]% apparently is to be used in the initial bulk distribution of Alesse.

Presently, the dosage of Alesse is 20 mcg of EE and a [redacted]% overage would make the dosage [redacted] mcg of EE. For LN, the dosage is 100 mcg, the overage would make the LN dosage 105 mcg. From a clinical viewpoint, it is my opinion, that this [redacted]% overage would not produce a significant clinical or safety issue. Therefore, it is safe to allow the release of the initial bulk distribution lots. It is my understanding, that after the inital bulk distribution is completed, the [redacted]% overage will be corrected for all subsequent lots to be distributed.

Phill H. Price, M.D.
March 25, 1997

Kush

NDA 20-683

Wyeth-Ayerst Laboratories
Attention: Mr. Douglas W. Bitz
Manager, Regulatory Affairs
P.O. Box 8299
PHILADELPHIA PA 19101

MAR 19 1997

Dear Mr. Bitz:

Please refer to your pending March 27, 1996, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alesse [levonorgestrel (100 mg)/ethinyl estradiol (20 mg)] tablets.

We have completed our review of the Clinical section of your submission and request you incorporate the following changes to your label:

Prescribing Information

INDICATIONS AND USAGE section

1. Third paragraph, next to last sentence, the words
should be deleted.

2. Third paragraph, last sentence, an estimate of the percentage of subjects who
should be provided.

WARNINGS section, subsection

This section should be revised to read:

ADVERSE REACTIONS section

In the fourth paragraph discussing adverse reactions the following four terms should be removed:

This decision is based on recommendations of a previous Fertility and Maternal Health Advisory Committee.

DOSAGE AND ADMINISTRATION section

Subsection third paragraph, fourth sentence

The descriptor should be removed. This sentence should now read:

Brief Patient Insert

At the end of this section, the following text should be inserted as the last paragraph:

Detailed Patient Labeling

EFFECTIVENESS OF ORAL CONTRACEPTIVES section

GENERAL PRECAUTIONS section

The following should be added as the fifth paragraph:

We would appreciate your prompt written response in the form of revised product labeling so that we may continue our evaluation of your NDA.

If you have any questions, please contact Ms. Christina Kish at (301) 827-4260.

Sincerely,

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Office Of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig. NDA
HFD-580
HFD-580/PPrice/HJolson
HFD-580/CKish/3.17.97/n20683ir.cl
concurrence:LPauls 3.18.97/PPrice 3.19.97/HJolson 3.19.97

INFORMATION REQUEST

K1511

NDA 20-683

MAR 13 1997

Wyeth-Ayerst Laboratories
Attention: Mr. Douglas W. Bitz
Manager, Regulatory Affairs
P.O. Box 8299
PHILADELPHIA PA 19101

Dear Mr. Bitz:

Please refer to your pending March 27, 1996, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alesse [levonorgestrel (100 mg)/ethinyl estradiol (20 mg)] tablets.

We have completed our review of the Clinical Pharmacology and Biopharmaceutics section of your submission and have the following comments and requests:

1. Please incorporate the enclosed changes to the CLINICAL PHARMACOLOGY section of your label.

2. Please submit a letter of commitment to conduct a Phase 4 bioequivalence study

   Please submit your bioequivalence protocol for review prior to initiation of the study.

We would appreciate your prompt written response so that we can continue our evaluation of your NDA.

If you have any questions, please contact Ms. Christina Kish at (301) 827-4260.

Sincerely,

Heidi Jolson for LR. 3/11/97
Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Office Of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE
Revisions to the CLINICAL PHARMACOLOGY
section of the labeling

cc:
Orig. NDA
HFD-580
HFD-580/ADorantes/LRarick
HFD-580/CKish/3.10.97/n20683ir.bp
concurrence:LPauls 3.10.97/ADorantes 3.10.97

INFORMATION REQUEST (IR)

NDA 20-683

JAN 30 1997

Wyeth-Ayerst Laboratories
Attention: Mr. Douglas W. Bitz
Manager, Regulatory Affairs
P.O. Box 8299
PHILADELPHIA PA 19101

Dear Mr. Bitz:

Please refer to your pending March 27, 1996, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alesse [levonorgestrel (100 mg)/ethinyl estradiol (20 mg)] tablets.

We have completed our review of the Chemistry, Manufacturing and Controls section of your submission and have identified the following deficiencies:

1. The average levonorgestrel strength in the three stability batches submitted is % or, if the % value is dropped, %. The average ethinyl estradiol strength is %. Please provide either documentation of the manufacturing losses to justify the % overage in the formulation submitted for the drug product, or revise the formulation to reduce or eliminate the overage based on the actual manufacturing data submitted.

2. Please provide information on the storage of the levonorgestrel and estradiol triturations before use and on the storage of the tablet cores before coating. Include descriptions of the container/closure systems used, the environmental conditions of storage (i.e., temperature and humidity) and any limits placed on the length of storage before use of the or tablet cores in succeeding manufacturing steps.

3. The information submitted for the in-process controls and test is deficient because you have only provided the actual specifications of the test in the Master Batch Record and reserved the right to modify the Master Batch Record "within the context of the regulatory method of manufacture." Please submit specifications for the in-process controls and tests.

4. You have not stated whether or not you propose to reprocess the material in the manufacturing process should it deviate from specifications. If reprocessing is proposed, then you will need to submit a brief summary of the proposed reprocessing procedures as well as information about maximum holding times and storage conditions before reprocessing and any additional controls used.

5. A deficiency letter under separate cover has been sent to holder of DMF for the Mini-Pack™ units used to package the drug product.

6. The **DOSAGE AND ADMINISTRATION** section of the prescribing information

7. The **HOW TO USE THE ALESSE MINI-PACK** section of the Detailed Patient Labeling should be revised

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Ms. Christina Kish at (301) 827-4260.

Sincerely,

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Office Of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig. NDA
HFD-580
HFD-580/MRhee/RSeevers/LRarick
HFD-222/YChiu
HFD-580/CKish/1.27.97/n20683ir.cm
concurrence:LPauls 1.28.97/RSeevers 1.29.97/MRhee 1.28.97

INFORMATION REQUEST (IR)

Co. Corres

WYETH-AYERST RESEARCH

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX (610)964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

March 26, 1997

NDA No. 20-683

Response to FDA Request:
Revised Draft Labeling

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Rarick:

Reference is made to NDA No. 20-683 for Alesse (levonorgestrel 100µg/ ethinyl estradiol 20µg), and to your March 19, 1997 letter requesting changes to the draft labeling. In response to that request, Wyeth-Ayerst is providing herewith a revised draft of the Prescribing Information, and a commitment to make the requested changes to the patient labeling, as detailed below. Listed below are specific responses to each of the labeling comments contained in your letter:

Prescribing Information

INDICATIONS AND USAGE Section:

1. The words, have been deleted from the third paragraph.

2. Information detailing the number and percentage of subjects who is provided at the end of this section.

WARNINGS Section, Subsection:

In a telephone conversation on March 25, 1997 among Dr. Rarick, Ms. Kish, and Mr. Joseph Sobecki of Wyeth-Ayerst, Dr. Rarick indicated that since the labeling of other approved oral contraceptives does not list specific incidences of intermenstrual bleeding in the subsection of the WARNINGS section, Wyeth-Ayerst could propose to retain the Class Labeling text of that subsection, as submitted in previous draft labeling (on December 20, 1996), so long as Wyeth-Ayerst does not quote numerical incidences of intermenstrual bleeding in promotional material for Alesse.

Accordingly, pending the issuance of industry-wide standards from FDA on this issue, Wyeth-Ayerst agrees that promotional statements on intermenstrual bleeding for Alesse will not contain numerical incidences (see Attachment A for "Sales Aid" page 7, as revised from the February 21, 1997 submission of proposed launch materials). We anticipate that any promotional practices to the contrary by other sponsors would be viewed unfavorably by the Division and DDMAC. Please note, however, that should data from adequate and well-controlled clinical studies become available in the future, which support claims of comparability in accord with usual DDMAC requirements, Wyeth-Ayerst may elect to employ such data in promotional materials.

In summary, the ' ' subsection of the WARNINGS section remains identical to our December 20, 1996 submission.

ADVERSE REACTIONS Section:

As requested, the following Adverse Reactions have been removed:

DOSAGE AND ADMINISTRATION Section:

1. Statements concerning pills have been added as the second and third sentences of this section.

2. In the middle of the 3rd-last paragraph of this section, has been removed from as requested.

The revised draft Prescribing Information labeling is provided as Attachment B.

Brief Patient Insert and Detailed Patient Labeling

The specific changes to the patient labeling that we commit to make at the next printing are as follows:

Brief Patient Insert

Detailed Patient Labeling

EFFECTIVENESS OF ORAL CONTRACEPTIVES Section:

GENERAL PRECAUTIONS Section:

Please note that packaging of the Prescribing Information has not yet occurred; all product to be distributed, including the initial launch quantities, will contain the Prescribing Information (physician labeling) as approved by FDA.

We believe that this response adequately addresses all of the items in the Division's letter of March 19, 1997. If you have any questions, please contact our representative, Mr. Joseph Sobecki, at (610) 902-3737, or the undersigned at (610) 902-3739.

Sincerely,

WYETH-AYERST LABORATORIES

Douglas W. Bitz
Director, U.S. Regulatory Affairs

Desk Copy: Ms. Christina Kish, Division of Reproductive and Urologic Drug Products

WYETH-AYERST RESEARCH

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX (610)964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

March 25, 1997

NDA No. 20-683

Response to FDA Request:
Phase IV Commitment

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Rarick:

Reference is made to the March 25, 1997 teleconference with Dr. Angelica Dorantes of the Division of Biopharmaceutics, concerning the nature of a Phase IV Commitment to address FDA concerns about the potential migration of , into Alesse tablets from the used to protect the product from light. In accordance with Dr. Dorantes' recommendation, Wyeth-Ayerst hereby commits to provide, within three months of NDA approval, comparative dissolution data as specified for SUPAC-IR Case C (60 FR 61639). Specifically, multi-point dissolution profiles will be performed in for: i) Alesse tablets that have been removed from the foil pouch and stored in for one month, and ii) Alesse tablets that have been removed from the foil pouch and stored without a at ambient conditions for one month, while protected from light. Sampling will be performed at minutes, or until % is dissolved of both levonorgestrel and ethinyl estradiol, or until an asymptote is reached. A surfactant will be used as appropriate.

If you have any questions, please contact our representative, Mr. Joseph Sobecki, at (610) 902-3737, or the undersigned at (610) 902-3739.

Sincerely,

WYETH-AYERST LABORATORIES

Douglas W. Bitz
Director, U.S. Regulatory Affairs

Desk Copy: Ms. Christina Kish, Division of Reproductive and Urologic Drug Products

TM-1380

ORIGINAL

WYETH-AYERST RESEARCH

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FAX: (610)964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

ORIG AMENDMENT

NDA No. 20-683

March 24, 1997

Response to FDA Request:
Batch Release Data- Alesse

Ms. Christina Kish, Consumer Safety Officer
Division of Reproductive and Urologic Drug Products (HFD-580)
Room 17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Dear Christina:

Reference is made to our March 18, 1997 telephone conversation concerning pending NDA No. 20-683 for Alesse (levonorgestrel 100 µg/ ethinyl estradiol 20 µg). In that conversation, you requested that Wyeth-Ayerst provide, via facsimile, "batch release" analytical data for the fourteen (14) product batches that have been manufactured with a [redacted]% overage. Please recall that, in our correspondence dated March 12, 1997, Wyeth-Ayerst had previously committed to eliminate the overage for future batches of Alesse, beyond the 14 that had already been manufactured in anticipation of product launch.

Attached are the requested results from batch release testing available to date, presented in a tabular format for your convenience. Please note that for all of the 14 batches, the assays are well within the [redacted]% limits, the content uniformity results are well within the USP specifications, and the other testing parameters meet the applicable NDA/ USP specifications. These batches were all manufactured using the same validated manufacturing procedure. The analytical results presented here demonstrate that these 14 batches are essentially equivalent in strength and content uniformity. The differences in the test results among the batches are within the normal variation expected due to sampling and assay reproducibility.

Please be aware that these batches have not yet been formally released, and are still pending QA review. Additionally, our Amendment of February 14, 1997 contained a typographical error [redacted] the Content Uniformity CV% for Batch A960312: the CV had been reported as [redacted]% but upon further review is actually [redacted]%." This does not change any of the conclusions made with respect to those data.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 25 1997
HFD-580

If you have any questions, or need any additional information, please don't hesitate to contact me at (610) 902-3737.

Sincerely,

Joseph J. Sobecki
Associate Director, U.S. Regulatory Affairs

ORIGINAL

WYETH-AYERST RESEARCH

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610)964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

March 12, 1997

Alesse™ tablets (levonorgestrel 100µg/
ethinyl estradiol 20µg)

NDA No. 20-683

**Amendment to a Pending New Drug Application:
Chemistry, Manufacturing, and Controls**

ORIG AMENDMENT

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAR 13 1997
HFD-580

Dear Dr. Rarick:

Reference is made to NDA No. 20-683 for Alesse™ tablets (levonorgestrel 100µg/ethinyl estradiol 20µg). Further reference is made to a telephone conversation on March 10, 1997 between Dr. Robert Seevers and Ms. Christina Kish of your Division, and Mr. Joseph Sobecki and Mr. Douglas Bitz of Wyeth-Ayerst.

In that conversation, Dr. Seevers commented that the data submitted in NDA No. 20-683 are not sufficient to justify the [redacted]% manufacturing overage proposed by Wyeth-Ayerst for the active ingredients in the Alesse™ product. Accordingly, Dr. Seevers requested that Wyeth-Ayerst submit a commitment to eliminate the [redacted]% overage for the active ingredients. He further stated that based on discussions he had with the Chemistry Team Leader (Dr. Moo Jhong Rhee), FDA would permit Wyeth-Ayerst to market the product batches already manufactured in anticipation of FDA approval and launch of the product, which include a [redacted]% overage.

In response to Dr. Seevers' request, Wyeth-Ayerst hereby commits to eliminate the [redacted]% manufacturing overage for the active ingredients in Alesse™ tablets (levonorgestrel and ethinyl estradiol), for any batch whose manufacture begins after the date of this letter. Based on the March 10, 1997 conversation with Dr. Seevers, it is expressly provided that Wyeth-Ayerst may market product from the fourteen (14) batches of tablets which have already been manufactured with a [redacted]% overage in anticipation of product launch, after testing and release of those batches.

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

If upon manufacturing a sufficient number of batches of Alesse™ tablets which do not employ any overage, Wyeth-Ayerst believes that the data support the need to reinstate an overage, a Supplemental Application will be submitted to justify such overage.

A revised copy of the Composition page in NDA No. 20-683 (Volume 1.2, page 24), on which the overage has been removed, is provided herein.

If you have any questions, please contact our representative Mr. Joseph Sobecki at (610) 902-3737, or the undersigned at (610) 902-3739.

Sincerely,

WYETH-AYERST LABORATORIES

Douglas W. Bitz
Director, U.S. Regulatory Affairs

Desk Copies: Dr. Robert Seevers, Division of Reproductive and Urologic Drug Products
Ms. Christina Kish, Division of Reproductive and Urologic Drug Products

ORIGINAL

WYETH-AYERST RESEARCH

NEW COR.

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610)964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

NEW CORRESP

No. 20-683
Alesse™ tablets (levonorgestrel 0.1mg/
ethinyl estradiol .02mg)

February 21, 1997

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Room 17B-20
Food and Drug Administration (HFD-580)
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Rarick:

Reference is made to the pending NDA No. 20-683 for Alesse™ 0.1mg levonorgestrel/.02mg ethinyl estradiol tablets, submitted on March 27, 1996.

In anticipation of a March approval of Alesse, Wyeth-Ayerst is providing the Division of Reproductive and Urologic Drug Products with a copy of the proposed core launch materials submitted to the Division of Drug Marketing, Advertising and Communications on February 21, 1997.

Should you have any questions regarding these proposed launch materials, please call the undersigned at (610) 902-3772 or Ms. Janice Barry at (610) 902-3784.

Sincerely,

WYETH-AYERST LABORATORIES

Joan E. Barton, Associate Director
Women's Health Care Products
U.S. Drug Regulatory Affairs

CENTER FOR DRUG RECEIVED FEB 24 1997 HFD-530 RESEARCH

Additional core launch materials including the press release will be forwarded to your attention in the near future.

A complete copy of these proposed launch materials has been forwarded to the Division of Reproductive and Urologic Drug Products.

Should you have any questions regarding these proposed launch materials, please call the undersigned at (610) 902-3772 or Ms. Janice Barry (610) 902-3784.

Sincerely,

WYETH-AYERST LABORATORIES

Joan E Barton

Joan E. Barton, Associate Director
Women's Health Care Products
U.S. Drug Regulatory Affairs

JKB/jkb/alsprm

WYETH-AYERST RESEARCH

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610)964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

February 20, 1997

Alesse™ tablets (levonorgestrel 100µg/
ethinyl estradiol 20µg)

NDA No. 20-683

Response to FDA Request
(Biopharmaceutics)

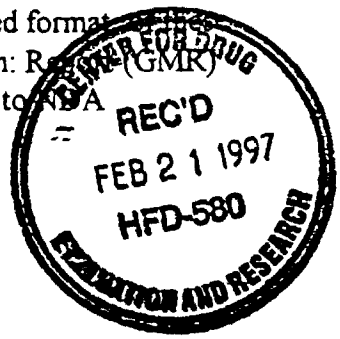
Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Rarick:

Reference is made to NDA No. 20-683 for Alesse™ tablets (levonorgestrel 100 µg/ ethinyl estradiol 20 µg), submitted on March 27, 1996. Further reference is made to our January 15, 1997 submission to NDA No. 20-683, which responded to a request from the Division of Biopharmaceutics for information comparing the bioavailability of levonorgestrel/ethinyl estradiol tablets with a reference solution or comparator product. In that submission, three such bioavailability studies were identified, which were conducted with the Wyeth-Ayerst levonorgestrel/ethinyl estradiol formulation marketed as Triphasil® (NDA Nos. 19-190 and 19-192).

In a February 13, 1997 telephone conversation between Ms. Christina Kish of your Division and Mr. Joseph Sobecki of Wyeth-Ayerst, Ms. Kish requested that Wyeth-Ayerst submit to NDA No. 20-683 brief summaries, in a recommended format, of those three Triphasil® bioavailability studies. Ms. Kish also asked that we submit a request for waiver of the requirement for bioavailability data directly comparing the Alesse™ formulation with a reference solution or comparator product.

In response to Ms. Kish's request, enclosed are summaries, in the recommended format, of three bioavailability studies which compare Triphasil® with a reference solution: R[illegible] (GMR). As noted in our January 15, 1997 submission to NDA



TH-1380

No. 20-683, the complete reports of these three studies were submitted in an April 21, 1988 Supplement (No. S-014) to NDA Nos. 19-190 and 19-192 for Triphasil®, which was approved on August 15, 1991.

Based upon the multiple-dose bioavailability study with Alesse™ included in NDA No. 20-683, the three comparative studies summarized herein which were conducted with Triphasil® , and the evidence provided in our January 15, 1997 submission that the Alesse™ and Triphasil® formulations are proportionally similar, Wyeth-Ayerst hereby requests a waiver of the requirement for submission of in vivo bioavailability data which directly compares the Alesse™ formulation with a reference material.

If you have any questions, please contact our representative, Mr. Joseph Sobecki, at (610) 902-3737, or the undersigned at (610) 902-3739.

Sincerely,

WYETH-AYERST LABORATORIES

Joseph J. Sobecki/For Douglas W. Bitz

Douglas W. Bitz
Director, U.S. Regulatory Affairs

Desk Copies: Dr. Angelica Dorantes, Division of Biopharmaceutics
Ms. Christina Kish, Division of Reproductive and Urologic Drug Products

JJS/lm:072

WYETH-AYERST RESEARCH

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610)964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

February 14, 1997

NDA No. 20-683

Alesse™ tablets (levonorgestrel 100 µg/ ethinyl estradiol 20 µg)

Response to FDA Request (Chemistry, Manufacturing and Controls)

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Rarick:

Reference is made to NDA No. 20-683 for Alesse™ tablets (levonorgestrel 100 µg/ethinyl estradiol 20 µg), submitted on March 27, 1996. Reference is also made to your January 30, 1997 letter, which requested additional information concerning the Chemistry, Manufacturing and Controls section of the NDA.

Provided herein are complete responses to all of the items outlined in your letter of January 30, 1997.

If you have any questions or need any additional information, please contact our representative, Mr. Joseph Sobecki at (610) 902-3737, or the undersigned at (610) 902-3739.

Sincerely,

WYETH-AYERST LABORATORIES

Joseph S. Sobecki for Douglas W. Bitz

Douglas W. Bitz
Director, U.S. Regulatory Affairs

Desk copies: Dr. Robert Seevers, Chemist, Division of Reproductive and Urologic Drug Products
Ms. Christina Kish, CSO, Division of Reproductive and Urologic Drug Products

JJS/lm:069

ORIGINAL

WYETH-AYERST *RESEARCH*

P.O. BOX 8299; PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610)964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

REVIEWS COMPLETED
ACTION:
LETTER N.A.I. MEMO
CSO INITIALS DATE

ORIG AMENDMENT

February 13, 1997

NDA No. 20-683

Alesse™ tablets (levonorgestrel 100 µg/ ethinyl estradiol 20 µg)

Response to FDA Request (Biometrics)

Noted by Dr. ... 3/3/97

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Rarick:

Reference is made to NDA No. 20-683 for Alesse™ tablets (levonorgestrel 100 µg/ethinyl estradiol 20 µg), submitted on March 27, 1996. Reference is also made to telephone conversations of February 12, 1997 and February 13, 1997 between Dr. Ananda Gubbi (Biometrician, Division of Metabolism and Endocrine Drug Products) and Mr. Joseph Sobecki of Wyeth-Ayerst. Dr. Gubbi requested diskettes containing the electronic data sets necessary to replicate the statistical analyses of the Pearl Index and life-table contained in the NDA.

Enclosed is a diskette containing the necessary data, provided in Excel 4.0 format, as requested. The data files are as follows:

For the convenience of the reviewer, also enclosed for ready reference are hard copies of the following relevant summary tabulations from the NDA:

In addition, a hard copy listing is included which contains the variable names and values that correspond with the data file.

If you have any questions or need any additional information, please contact our representative, Mr. Joseph Sobecki at (610) 902-3737, or the undersigned at (610) 902-3739.

Sincerely,

WYETH-AYERST LABORATORIES

Joseph S. Sobecki for Douglas W. Bitz

Douglas W. Bitz
Director, U.S. Regulatory Affairs

Desk copies: Dr. Ananda Gubbi, Biometrician (complete copy with diskette)
Ms. Christina Kish, CSO, (cover letter only via fax)

JJS/lm:068

WYETH-AYERST RESEARCH

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610)964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

January 30, 1997

Alesse™ tablets (levonorgestrel 100µg/
ethinyl estradiol 20µg)

NDA No. 20-683

**Response to FDA Request:
(Chemistry, Manufacturing
and Controls)**

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr Rarick:

Reference is made to NDA No. 20-683 for Alesse™ tablets (levonorgestrel 100µg/ ethinyl estradiol 20µg), submitted March 27, 1996, and to a chemistry, manufacturing and controls amendment submitted on December 20, 1996. Reference is also made to two telephone calls on January 13, 1997 from Ms. Christina Kish and Dr. Robert Seevers of the Division, to Mr. Joseph Sobecki of Wyeth-Ayerst.

Ms. Kish asked whether Wyeth-Ayerst had (i) performed chemical testing to characterize placebo tablets , and (ii) whether the (intended for use by the patient to protect the product from light) had been used in clinical trials. Our responses to those questions are provided herein.

With regard to fading of the placebo tablets, please note that the placebos are *exactly* the same as those included with our marketed oral contraceptive product, Triphasil (NDA No. 19-190). We further remind the Division that in Supplement No. 024 to NDA No. 19-190 (dated January 15, 1992), which provided for use of the minipacks and wallets to package that product, data were provided which demonstrated that the placebos fade upon exposure to intense light (Vol. 1 of 1, page 152). In fact, those data are virtually identical to the corresponding placebo data submitted in the Alesse™ NDA (Vol. 1.3, page 220), as would be expected. The Triphasil supplement contained pouch and carton labeling that is consistent with that for Alesse™, with both stating " protect from light by storing dial dispenser in the folder provided." This supplement, including the data concerning fading, was approved on March 9, 1993.

In summary, the placebo tablets, and their corresponding packaging and labeling, are already approved by FDA for Triphasil, and are identical to those for Alesse™

Additionally, Dr. Seevers inquired as to whether the migration of wallets into the Alesse™ tablets could potentially affect the absorption of the active ingredients. As a means of addressing this issue, Wyeth-Ayerst has conducted dissolution testing of Alesse™ tablets which were exposed to, and absorbed, quantities of far in excess of those seen in the NDA stability studies. The results of this testing, also described herein, show that has *no impact* on release of the active ingredients from the Alesse™ tablets, nor does absorption of affect the product's potency or purity.

Further, please note that the same wallets (in a different color) have been used commercially for our marketed oral contraceptive product, Triphasil (NDA No. 19-190) since mid-1994. A review of spontaneous adverse drug experience (ADE) reporting for Triphasil shows *no increase* in the rate of reported unintended pregnancies for 1996 (when wallets were used), compared to 1993 (before wallets were used). In addition, we have also conducted a review of the labeling for marketed over-the-counter (OTC) drug products containing etc.), and have found no Contraindications, Warnings, or Precautions concerning concomitant use of these containing OTC products with oral contraceptives. Most notably, no such labeling statements are required for containing OTC Oral Discomfort (Relief) Products, according to the Tentative Final Monograph (56 FR 48302).

It is our conclusion that any minuscule levels of which could potentially migrate from the into Alesse™ tablets pose no safety or efficacy concerns.

If you have any questions, please contact our representative, Mr. Joseph Sobecki, at (610) 902-3737, or the undersigned at (610) 902-3739.

Sincerely,

WYETH-AYERST LABORATORIES

Douglas W. Bitz
Director, U.S. Regulatory Affairs

Desk Copies: Dr. Robert Seevers, Division of Reproductive and Urologic Drug Products
Ms. Christina Kish, Division of Reproductive and Urologic Drug Products

JJS 067

ORIGINAL

WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

January 15, 1997

Alesse™ tablets (levonorgestrel 100µg/ ethinyl estradiol 20µg)

ORIG AMENDMENT

NDA No. 20-683

Response to FDA Request (Biopharmaceutics)

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

Dear Dr. Rarick:

Reference is made to a December 23, 1996 telephone conversation between Dr. Angelica Dorantes of the Division of Biopharmaceutics and Mr. Joseph Sobecki of Wyeth-Ayerst. During that conversation, Dr. Dorantes requested information comparing the bioavailability of levonorgestrel/ethinyl estradiol tablets with that of a reference solution or comparator product.

In response to Dr. Dorantes' request, attached is information referencing three such studies, which were conducted with the Wyeth-Ayerst levonorgestrel/ethinyl estradiol formulation marketed as Triphasil® (NDA Nos. 19-190 and 19-192). Based upon the results of those studies, and because the Alesse™ (levonorgestrel 100µg/ethinyl estradiol 20µg) formulation is proportionally similar to Triphasil®, it was determined that a separate study directly comparing Alesse™ to a reference solution is unnecessary, and would provide no relevant additional information.

A copy of this response has been faxed to Dr. Dorantes, and Desk Copies have also been provided to Dr. Dorantes and Ms. Christina Kish. If you have any questions, please contact our representative Mr. Joseph Sobecki at (610) 902-3737, or the undersigned at (610) 902-3739.

Sincerely,

WYETH-AYERST LABORATORIES

Joseph S. Sobecki for Douglas W. Bitz

Douglas W. Bitz
Director, U.S. Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 16 1997
HFD-580

/lm:064

Desk Copies: Dr. Angelica Dorantes, Division of Biopharmaceutics
Ms. Christina Kish, Division of Reproductive and Urologic Drug Products

WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

December 20, 1996

NDA No. 20-683

Amendment to a Pending New Drug Application:
Chemistry, Manufacturing, and Controls

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Rarick:

Reference is made to NDA No. 20-683 for Alesse™ tablets (levonorgestrel 0.100 mg/ethinyl estradiol 0.020 mg), submitted on March 27, 1996.

We are providing information to update or correct certain Chemistry, Manufacturing, and Controls documentation in the original NDA submission, as follows:

1. In a letter dated October 8, 1996 from Mr. Nicholas Falcone of the FDA Philadelphia District Laboratory, FDA requested that we submit samples and associated materials for methods validation testing by two FDA District Laboratories. In preparing the submission of the requested samples, Wyeth-Ayerst realized that the ethinyl estradiol reference standard required revalidation testing. As a result, an updated Certificate of Analysis was prepared for the standard, and was provided, along with the applicable chromatograms and spectra, to the District Laboratory. These documents are provided as **Attachment 1**.

2. To assist the FDA District Laboratory in identifying degradant peaks in the chromatogram, Wyeth-Ayerst provided a control sample solution containing the degradants, along with information about its composition, and a representative chromatogram identifying the peaks. For your information, the details about the control sample are included as **Attachment 2**.

3. The analytical method for finished product degradation testing ; NDA No. 20-683, Volume 1.3, pages 89-96) has been updated to ensure that the analyst takes appropriate and necessary precautions to prevent extraneous peaks from developing due to sample and

equipment preparation. The updated method, which was provided to the FDA District Laboratory along with the samples, is included as **Attachment 3**.

4. In the Drug Product Container-Closure System section of the NDA (Volume 1.2, page 237), the PVC material to be used for the blister package domes was described as being [redacted] mil thick. It is not Wyeth-Ayerst's intention to restrict the thickness of the blister material to exactly [redacted] mil, but rather that PVC films of [redacted] mil or thicker may be used. Therefore, a corrected page 237 is provided as **Attachment 4**. This change, to allow a heavier gauge PVC than the [redacted] mil used to package the product used for the stability studies, has no adverse impact on product stability.

5. In the stability report provided in the NDA (GTR #25643; Volume 1.3, pages 166-167), it was indicated that due to the potential for migration of trace levels of into the Alesse tablets from the "wallet" that is to be used by the patient to protect the MINI-PACK™ or blister pack from light, alternative protective coverings would be recommended. However, after further extensive evaluation, it has been concluded that the wallets originally proposed are, in fact, acceptable for use. **Attachment 5** provides details on all testing and supporting information leading to this determination.

If there are any questions concerning this submission, please contact our representative, Mr. Joseph Sobecki, at (610) 902-3737, or the undersigned at (610) 902-3739.

Sincerely,

WYETH-AYERST LABORATORIES

Douglas W. Bitz
Director
U.S. Regulatory Affairs

Submitted in duplicate
Desk Copy (letter): Ms. Christina Kish, CSO
Dr. Robert Seavers, Chemistry Reviewer

WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

December 20, 1996

U.S. REGULATORY AFFAIRS
NDA No. 20-683

Amendment to a Pending New Drug Application: Revised Draft Labeling

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Center for Drug Evaluation and Research
Attn: Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Rarick:

Reference is made to NDA No. 20-683 for Alesse™ (levonorgestrel 100µg/ethinyl estradiol 20µg), submitted on March 27, 1996.

We are aware that FDA is in the process of standardizing the content and presentation of the information in the "Pharmacokinetics" subsection of the CLINICAL PHARMACOLOGY section of the physician package insert. Specifically, FDA has been requesting sponsors to reorganize that subsection to present the information under subheadings entitled, *Absorption, Distribution, Metabolism, and Excretion,* followed by a subsection entitled "Special Populations," which is to include appropriate pharmacokinetic information under subheadings entitled *Race, Renal Insufficiency, Hepatic Insufficiency, and Drug-Drug Interactions.*

In conversations in early September 1996, between Ms. Christina Kish of your Division and Mr. Douglas Bitz of Wyeth-Ayerst, it was agreed that Wyeth-Ayerst would revise the "Pharmacokinetics" subsection of the Alesse™ draft labeling, and submit the updated labeling when available. Accordingly, enclosed is the revised annotated physician package insert.

Other than the CLINICAL PHARMACOLOGY section, the only differences between this revised labeling and that submitted in the original NDA are:

If there are any questions regarding this submission, please contact our representative Mr. Joseph J. Sobecki at (610) 902-3737

Sincerely,

WYETH-AYERST LABORATORIES

Douglas W. Bitz
Director, U.S. Regulatory Affairs

Attachment: 4 Copies Draft Labeling
Desk Copy (Letter): Ms. Christina Kish, CSO
Dr. Angelica Dorantes, HFD-426

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WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

October 3, 1996

Alesse™ tablets (levonorgestrel 0.100mg/ ethinyl estradiol 0.020mg)

NDA No. 20-683

Amendment to a Pending Application: Safety Update

Lisa Rarick, MD, Acting Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Rarick:

Reference is made to NDA No. 20-683 for Alesse™ tablets (levonorgestrel 0.100 mg/ethinyl estradiol 0.020 mg), submitted on March 27, 1996.

We are submitting herewith, pursuant to 21 CFR 314.50(d)(5)(vi)(b), a Safety Update Report for NDA No. 20-683. This submission is contained in a total of 12 volumes, comprised of an integrated summary (1 volume); supportive clinical pharmacology reports (1 volume) and the associated new case report tabulations (4 volumes); and new case report forms for subjects who discontinued due to an adverse event or pregnancy (6 volumes).

Please recall that the original NDA was prepared using a data cutoff date of June 30, 1995 for the ongoing safety and efficacy study . The clinical database from that study, as contained in the original NDA, included data for 1,477 women, with a total of cycles of experience; 792 of these women had completed 6 cycles of use. The enclosed Safety Update Report was prepared using a data cutoff date of March 29, 1996, and includes data from 1,665 women, with a total of cycles. These data represent an additional 188 enrolled subjects, and approximately a doubling of the total cycles of exposure. Accordingly, the cumulative safety data are the focus of this Safety Update.

The additional data reported herein support the safety profile of Alesse™ as presented in the original NDA; therefore, no changes are proposed to the draft labeling submitted in the original NDA as a result of this report.

Please note that in a July 9, 1996 telephone conversation between Ms. Christina Kish of your Division and Mr. Joseph Sobecki of Wyeth-Ayerst, Ms. Kish indicated that it would be reasonable to submit a single Safety Update Report to this NDA in early October, 1996.

If there are any questions concerning this submission, please contact our representative, Mr. Joseph Sobecki, at (610) 902-3737, or the undersigned at (610) 902-3739.

Sincerely,

WYETH-AYERST LABORATORIES

Douglas W. Bitz
Director, U.S. Regulatory Affairs

S/lm:046

WYETH-AYERST LABORATORIES

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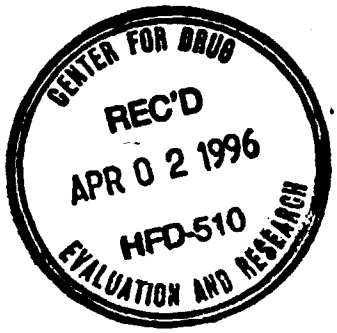
Division of American Home Products Corporation

REGULATORY AFFAIRS

Reviewed 8/16/96

March 27, 1995 96

Alesse™ Tablets
(levonorgestrel 0.100 mg/ethinyl estradiol 0.020mg)
NDA No. 20-683



Solomon Sobel, MD, Director
Division of Metabolism and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Central Document Room
Park Building, Room 214
12420 Parklawn Dr.
Rockville, MD 20852

Dear Dr. Sobel:

In accordance with 21 CFR §314.50, Wyeth-Ayerst is submitting a New Drug Application for Alesse™ Tablets (levonorgestrel 0.100 mg/ethinyl estradiol 0.020mg), NDA No. 20-683.

This low-dose formulation of levonorgestrel and ethinyl estradiol is indicated for the prevention of pregnancy in women who elect to use this product as a method of contraception, and is proposed for marketing in standard 21-day and 28-day (7 days of placebo) regimens.

The clinical development plan for this low-dose oral contraceptive (OC) product was submitted to FDA for review and comment on December 28, 1993 (IND This development plan provided for the submission of an NDA based on clinical data from at least 600 women who had completed 6 months of use, in accordance with the Division's 1987 OC clinical data requirements for products containing reduced amounts of approved steroids in the same ratio as a marketed product. On February 8, 1994, representatives of Wyeth-Ayerst discussed this clinical development plan with Dr. Phill Price (Medical Officer), and jointly reached agreement on the final design of the Wyeth-Ayerst clinical studies that comprise this NDA.

One (1) ongoing multicenter Phase III clinical trial provides the primary evidence for the efficacy and safety of Alesse. The clinical database derived from this study and presented in this NDA includes data for 1,477 women with a total of cycles of experience; 792 of these women have completed 6 cycles of use. Five (5) pregnancies occurred during the cycles evaluable for efficacy, for a Pearl Index of 0.84, indicating that Alesse is an effective low-dose oral contraceptive.

Additionally, Wyeth-Ayerst requests that the Division review the proposed trade name "Alesse™" for acceptability as early as possible, since there are several rate-limiting activities critical to the timely introduction of this new low dose OC which hinge on the finalization of the trade name. It is our understanding that the reviewing chemist is the primary liaison with the Labeling and Nomenclature Committee on this matter.

The Alesse NDA is organized into 99 volumes, as follows:

Item No.	Description	Volume No.
1	Index	1.1
2	Summary	1.1
3	Chemistry, Manufacturing, and Controls	1.2 - 1.8
4	Methods Validation/Draft Labeling	1.9 - 1.10
5	Nonclinical Pharmacology/Toxicology	1.11 - 1.14A
6	Human Pharmacokinetics and Bioavailability	1.15 - 1.20
8	Clinical	1.21 - 1.32
10	Statistical	1.33 - 1.38*
11	Case report Tabulations	1.40 - 1.97
12	Case Report Forms	1.98 - 1.99
13	Patent Information	1.1
15	Certification: Preapproval Inspection Requirements	1.1
	Certification: Generic Drugs Enforcement Act of 1992	1.1

* Due to an administrative oversight, there is no Volume 1.39.

In accordance with 21 CFR §314.50 (d)(1)(v), a field copy of the Chemistry, Manufacturing and Controls section (Item 3), the application form (356h), and the Application Summary (Item 2) was sent to the Philadelphia District Office, the FDA home district office for Wyeth-Ayerst Laboratories.

A check for which is 50% of the total User Fee required for an NDA submitted in Fiscal Year 1996 that contains clinical data, has been sent to the Food and Drug Administration c/o Mellon Bank, Pittsburgh, PA. User Fee I.D. #2927 has been assigned to this NDA.

If there are any question regarding this application, please contact the undersigned at (610) 902-3739.

Sincerely,

WYETH-AYERST LABORATORIES

Douglas W. Bitz
Director
U.S. Regulatory Affairs

MJM/lm:352