# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 20-683

## ADMINISTRATIVE DOCUMENTS

NDA No. 20-683

## PATENT INFORMATION UNDER SECTION 505(b)

In the opinion of the applicant and to the best of the applicant's knowledge, there is no U.S. Patent covering ALESSE™ (levonorgestrel, 0.100 mg and ethinyl estradiol, 0.020 mg tablets) monophasic regimens (21 days per cycle and 21 days per cycle plus 7 days placebo) or any use of the drug for which the applicant is seeking approval.

WYETH-AYERST LABORATORIES

By: _____

Arnold S. Milowsky
Patent Attorney

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-683 Trade (generic) names Alesse (ethinyl estradiol 0.020mg/levonorgestrel 0.100mg) tablets

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

____ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Signature of Preparer

3/20/92
Date

cc: Orig NDA
HFD-___/Div File
NDA Action Package

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

NDA No. 20-683

**ITEM 15 B. GENERIC DRUG ENFORCEMENT ACT OF 1992 CERTIFICATION STATEMENT**

Wyeth-Ayerst hereby certifies that it did not and will not knowingly use in any capacity the services of any person debarred under subsections (a) or (b) of section 306 of the Federal Food, Drug, and Cosmetic Act in connection with NDA 20-683 for Alesse™.

Signed: _____ Date: 3/11/98

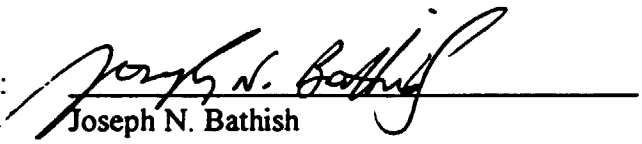
Joseph N. Bathish,
Vice President
Worldwide Regulatory Affairs

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

NDA No. 20-683

**Item 15 A. Certification Required by New Drug and Abbreviated New Drug Applications Preapproval Inspection Requirements**

The undersigned certifies that Wyeth-Ayerst has provided a true copy of the Chemistry, Manufacturing and Controls section, application form and application summary of NDA No. 20-683 for Alesse™ to the Philadelphia District Office, the FDA home district office for Wyeth-Ayerst Laboratories, as required under 21 CFR § 314.50 (d)(l)(v).

Signed: 

Joseph N. Bathish
Vice President
Worldwide Regulatory Affairs

## Group Leader Memorandum

| | |
|---|---|
| **NDA:** | **20-683** |
| **Drug and indication:** | **Alesse™ (levonorgestrel and ethinyl estradiol) for pregnancy prevention** |
| **Dose:** | **levonorgestrel 0.10 mg and ethinyl estradiol 0.02 mg daily for 21 out of each 28 day cycle** |
| **Applicant:** | **Wyeth-Ayerst** |
| **Submission received:** | **March 27, 1996** |
| **Date of MO review:** | **March 11, 1997** |
| **Date of Memorandum:** | **March 20, 1997** |

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In this application, the sponsor requests approval for a 21 day (and 28 day with 7 days of placebo) regimen of a monophasic oral contraceptive combination containing levonorgestrel 0.10 mg and ethinyl estradiol 0.02 mg. This oral contraceptive has the same 5:1 ratio of levonorgestrel and ethinyl estradiol as does another approved oral contraceptive from this sponsor (Nordette), but it contains lower doses of each active component. In support of this request, the sponsor has submitted the results of an open-label, uncontrolled trial conducted in the United States and Canada in 1,665 women who have contributed cycles of experience. The original NDA submission contained experience from 1,477 women (with cycles); the safety update reported the enrollment of an additional 188 women and an additional cycles of experience.

I concur with Dr. Price, the primary medical reviewer that this application is approvable and that the efficacy and safety profile of this product are comparable to other products in its class. Outstanding issues at the time of this regulatory action include the following:

**1. Overage**

As noted in the CMC review, this product has been manufactured with [redacted]% overage of the active ingredients. This overage, which was to allow for loss during manufacturing, is present in 14 batches that are intended for launch following NDA approval. However, because the clinical trial was conducted with a product manufactured with the same [redacted]% overage, there is no concern related to the safety and efficacy of these 14 batches.

After internal discussion in the division, it was decided that it was reasonable to allow the sponsor to launch these batches with the original labeling (stating % rather than

the actual % content) because the difference was small (1%) and was judged to be of no clinical importance. Further, the sponsor has committed to revising the composition of future batches to eliminate the 1% overage and to provide a certificate of analysis for the 14 batches showing that they meet the assay and content uniformity specifications of the NDA.

**2. Phase IV request for a bioequivalence study using pills stored in wallet**
Placebo pills in the 28 day formulation have been shown to fade on exposure to light. Accordingly, the sponsor recommends that the pills be stored in a wallet to avoid this fading. The Biopharmaceutics review has raised the question of whether the migration of from the wallet into the Alesse tablets could potentially affect the absorption of the active ingredients. To address this concern, the sponsor has provided dissolution data and has additionally committed to performing a bioequivalence study during Phase IV comparing the rate and extent of absorption of the two active ingredients using wallets for 21 days (as for the to-be-marketed product) and without wallets (as used in the pK and the clinical studies).

**3. Labeling**
In general, the proposed label follows the August 1994 'Labeling Guidance Text for Combination Oral Contraceptives'. However, the sponsor has been asked to revise their label to address the following clinical issues:

Heidi Jolson M.D.
Heidi M. Jolson, M.D., M.P.H.
Deputy Division Director, HFD-580

cc:
NDA20-683
HFD-580/LRarick/PPrice/HJolson

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NDA 20-683
Alesse (ethinyl estradiol 0.02 mg/
levonorgestrel 0.100 mg) Tablets
Wyeth-Ayerst Laboratories

**Safety Update Review**

The Safety Update Review will be included in the Medical Officers review of this application.

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**Advisory Committee Meeting Minutes**

This application was not the subject of an Advisory Committee meeting.

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**Federal Register Notice**

This application was not the subject of a Federal Register Notice.

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## Advertising Materials

Advertising materials have not yet been submitted for this application.