CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

83-723/S018

Trade Name: PREMARIN Vaginal Cream, 0.625 mg/g

Generic Name: (conjugated estrogens)

Sponsor: Wyeth-Ayerst Laboratories.

Approval Date: December 17, 1985

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-723/S018

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL LETTER

83-723/S018

6.1

ANDA 83-273/S-018

DEC 17 1985

Ayerst Laboratories
Division of American Home Products Corporation
Attention: John Rapoza, M.S., R.Ph.
685 Third Avenue
New York, NY 10017

Dear Mr. Rapoza:

Reference is made to your supplemental new drug application submitted pursuant to Section 314.70 of the Regulations, dated October 15, 1985, regarding your abbreviated new drug application for Premarin (conjugated estrogens) Vaginal Cream, 0.625 mg/g.

We refer also to our letter of November 18, 1985.

b(4) The supplemental application provides for a reduction of the amount of [redacted] in Pregnant Mares Urine (PMU) used to manufacture conjugated estrogens, U.S.P.

We have completed the review of this supplemental application and it is approved. Our letter of October 16, 1978, detailed the conditions relating to the approval of this abbreviated application.

The material submitted is being retained as part of your application.

Sincerely yours,

Kenneth C. Johnson FOR 12-17-85

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc: BKL-DO
HFN-230
HFN-234
HCZell/LDavidson 12/16/85
r/d init HCZell/MSeife HCZell 12/16/85
v dore 12/13/85 (0079)
APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-723/S018

CHEMISTRY REVIEW(S)

NDA 83-273 CHEMIST'S REVIEW FOR ANDA OR SUPPLEMENT

NAME AND ADDRESS OF APPLICANT:
Ayerst Laboratories
New York, NY 10017

PURPOSE OF SUPPLEMENT S-018
To provide for a reduction in the amount of [redacted] b(4)
in Pregnant Mares Urine (PMU) used to manufacture conjugated estrogens, USP.

DATE OF SUBMISSION
10/15/85

PHARMACOLOGICAL CATEGORY
Estrogen

NAME OF DRUG
Premarin

HOW DISPENSED
Rx

DOSAGE FORM
Vaginal Cream

POTENCY
0.625 mg/g

STERILIZATION
NC

SAMPLES
N/A

RELATED IND/NDA/DMF
85-515
87-824
4-782 (Premarin Tablets)

LABELING
NC

BIOLOGIC AVAILABILITY
N/A

ESTABLISHMENT INSPECTION
N/A

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS: Satisfactory. (See 11/15/85 Review) As per attached review from M. Bennett (HFN-810) based on the attached microbiological review from Richard Norton (HFN-815), the reduction in [redacted] is adequately justified and is satisfactory. b(4)

PACKAGING
NC

STABILITY
Protocol: NC

Exp. Date: NC (24 month)

REMARKS AND CONCLUSION
Approval letter should issue.
LDavidson 12/10/85 HCZell 12/11/85 (0079v)
LDavidson 12/16/85 HCZell 12/16/85

2 Page(s) Withheld

1 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

83-273/S018
Chem Review

NDA 83-273 CHEMIST'S REVIEW FOR ANDA OR SUPPLEMENT

NAME AND ADDRESS OF APPLICANT:

Ayerst Laboratories
New York, New York 10017

PURPOSE OF AMENDMENT/SUPPLEMENT

To provide for a reduction the amount of [redacted] in Pregnant Mares Urine (PMU) used ~~by~~ manufacture conjugated estrogens, USP. b(4)

DATE(S) OF SUBMISSION(S)

10/15/85

PHARMACOLOGICAL CATEGORY	NAME OF DRUG	HOW DISPENSED
Estrogen	Premarin (Conjugated Estrogen)	Rx

DOSAGE FORM	POTENCY	STERILIZATION
Vaginal Cream	0.625 mg/g	NC

SAMPLES	RELATED IND/NDA/DMF
N/A	85-515, 87-824, 4-782 (Premarin)

LABELING

NC

BIOLOGIC AVAILABILITY

N/A

ESTABLISHMENT INSPECTION

N/A

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

Unsatisfactory
HFN-810 has a similar supplement to their application, 4-782/S-060, Premarin.- Martin Bennett has referred the supplement to Dr. Norton in HFN-815 for a microbiology consult. Parallel amendments will be required to make a uniform Agency decision. Firm is requesting a reduction b(4)
[redacted] in the amount of [redacted] in Pregnant Mares Urine b(4)
(PMU) used to manufacture conjugated estrogens, USP. Data was provided on the microbiological preservative effectiveness of the reduced levels. Waiting results of consult and HFN-810 decision.

PACKAGING

NC

STABILITY

Protocol: NC
Exp. Date: NC (24 months)

REMARKS AND CONCLUSION

Rev. W/F letter should issue requesting parallel amendments to that requested by HFN-810 and advising firm on consult with microbiologist.

LDavidson/11/14/85 HCZell/11/14/85

L Davidson 11/15/85
HC Zell 11/15/85

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-273/S018

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

November 20, 1985

Supervisory Chemist, Chief Branch II, HFN-234
Division of Generic Drugs

Premarin (Ayerst) - Manufacturing change-Uniformity of Reviews and Requests for Additional Information

Supervisory Chemist, HFN-810
Division of Metabolism and Endocrine Drug Products

We have, in the Division of Generic Drugs, HFN-230, a supplement (S-018) to ANDA 83-273, Premarin Vaginal Cream, which provides for a reduction in the amount of [redacted] in Pregnant Mares Urine which is used to manufacture Conjugated Estrogens, USP.

b(4)

It has come to our attention via Ayerst that a similar supplement exists in HFN-810.

I have spoken to Mr. Martin Bennett and learned that he has such a supplement (S-050) for NDA 4-782. Mr. Bennett informed me that he has requested a microbiological consult with regard to the data submitted. The same data has been submitted to HFN-230.

The purpose of this memo is to request that you and Mr. Bennett coordinate your reviews and decisions with us so that we will issue letters which are requesting the same or similar information and that you inform us when you have reached the approval stage of your supplement. The chemist in this Branch who is working on this supplement is Ms. Lynn Davidson (443-1390).

We have written a letter (attached) to Ayerst addressing the idea of coordinating the reviews.

If possible, I would appreciate your including a copy of this memo and the attached letter into NDA 4-782 so that Mr. Bennett will be alerted to let us know when he has reached any conclusions with regard to the subject of this memo.

Howard C. Zell, Ph.D.

HCZ/ms

Attachment: Review waiting/firm letter 83-273/S-018

cc: HFN-230/HSeife
HFN-234/HZell
ANDA 83-273 ✔
HFN-810/Sobel
HFN-810/MBennett

ANDA 83-273/S-018

Ayerst Laboratories
Division of American Home Products Corporation
Attention: John R. Rapoza, M.S., R.Ph.
685 Third Avenue
New York, New York 10017

NOV 18 1985

Dear Sir:

Reference is made to your supplemental new drug application submitted pursuant to Section 314.70 of the Regulations, dated October 15, 1985, regarding your abbreviated new drug application for Premarin (conjugated estrogens) Vaginal Cream, 0.625 mg/g.

The supplemental application provides for a reduction of the amount of [redacted] in Pregnant Mares Urine (PMU) used to manufacture conjugated estrogens, USP. b(4)

We have reviewed the material submitted and note that this supplement was also submitted to HFN-810 for Premarin Tablets, NDA 4-782/S-060. We are coordinating our review with the Division of Metabolism and Endocrine and will require the same amendments, if pertinent, as may be requested by HFN-810. We are awaiting the results of their review and will correspond further when we receive it.

The material submitted is being retained in our files.

Sincerely yours,

Kenneth L. Johnson for 11-18-85

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc:
BKL-DO
HFN-230
HFN-234
HZell/LDavidson/gp/11/15/85
R/d init. by: LDavidson/HCZell

L Davidson 11/15/85

HC Zell 11/15/85

REV W/F
0300g

Orig

SUPPLEMENT--EXPEDITED REVIEW REQUESTED

Ayerst®

AYERST LABORATORIES
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

685 Third Avenue / New York, N.Y. 10017 / Tel: (212) 878-5954 / Cable: ALPHAMIN, New York

JOHN R. RAPOZA, M. S., R. PH.
ASSISTANT VICE PRESIDENT
REGULATORY AFFAIRS

October 15, 1985

Marvin Seife, M.D.
Director
Division of Metabolism and Endocrine Drug Products (HFN-230)
Office of Biologic Research and Review
ATTN: DOCUMENT CONTROL ROOM 1670
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA NO. 83273 REF. NO. 5/018
NDA SUPPL FOR Mfg Rev

SUBJECT: ANDA 85-515; Premarin(R) (conjugated estrogens, U.S.P.) and methyltestosterone tablets
ANDA 83-273; Premarin (R) (conjugated estrogens, U.S.P.) Vaginal Cream ✓

Dear Dr. Seife:

Pursuant to 21 CFR 314.70, we are submitting in duplicate, a supplement to the subject NDA.

This supplement provides for using a reduced amount of [redacted] b(4) in Pregnant Mares Urine (PMU), which is used to manufacture conjugated estrogens, U.S.P. The NDA currently states that a [redacted] concentration is used. This supplemental NDA provides for a range between [redacted] b(4) b(4)

To document this change, please find the following:

Exhibit I--[redacted] b(4) revised to include the new [redacted] b(4)

Exhibit II--[redacted] documenting the microbiological [redacted] effectiveness of reduced levels [redacted] b(4) b(4)

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential materials is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 and/or 21 U.S.C., Section 331(j).

Sincerely,

for John Rapoza, M.S., R. Ph.

RECEIVED
OCT 16 1985
GENERIC DRUGS

JRR
DZ/bp

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SEVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date; May 31, 1986.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 C.F.R. Part 314).*

NAME OF APPLICANT	DATE OF SUBMISSION
Ayerst Laboratories	October 15, 1985
ADDRESS *(Number, Street, City, State and Zip Code)*	**TELEPHONE NO.** *(Include Area Code)*
685 Third Avenue New York, NY 10017	212-878-5000

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)*
ANDA 83-273

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Conjugated estrogens, U.S.P.	Premarin Vaginal Cream

CODE NAME *(If any)*	CHEMICAL NAME

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Cream	Intervaginally or topically	0.625 mg/g

PROPOSED INDICATIONS FOR USE

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION:

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)*

☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION *(ANDA) (21 CFR 314.55)*

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION *(Check one)*

☐ ORIGINAL APPLICATION

☐ AN AMENDMENT TO A PENDING APPLICATION

☐ RESUBMISSION

☒ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)*

☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*