CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-992

CHEMISTRY REVIEW(S)

DLIN
NOV 19 1998

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580
Review of Chemistry, Manufacturing and Controls

NDA #: 20-992
CHEMISTRY REVIEW #: 1

DATE REVIEWED: 06-NOV-1998
revised 19-NOV-1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	30-MAR-98	30-MAR-98	03-APR-98
Amendment	07-MAY-98	08-MAY-98	12-MAY-98
Amendment	19-JUN-98	22-JUN-98	26-JUN-98
Amendment	22-SEP-98	23-SEP-1998	06-OCT-98

NAME & ADDRESS OF SPONSOR: Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, OH 45213

DRUG PRODUCT NAME:

Proprietary:	Cenestin Tablets
Nonproprietary/Established/USAN:	Synthetic conjugated estrogens Tablets
Code Name/#:	
Chem.Type/Ther.Class:	3S

PARMACOLOGICAL CATEGORY/INDICATION: Estrogen/Treatment of Post Menopausal Vasomotor Symptoms

DOSAGE FORM: Tablet
STRENGTHS: 0.3, 0.625, 0.9, 1.25, 2.5 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: x Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

The active drug substance for this product is composed of a 9 component estrogen mixture:
See the following pages for the chemical names, structural formulas, molecular formulas and molecular weights.

CONCLUSIONS & RECOMMENDATIONS:

This NDA is approvable pending satisfactory resolution of the issues delineated in the draft letter. In addition, the establishment evaluations must be completed, with satisfactory results for all facilities.

cc:
Orig. NDA #20-992
HFD-580/Division File
HFD-580/DMoore
HFD-580/MRhee/DLin

R/D Init by: 11/19/98
filename: nda20992.1 (doc)

11/19/98
David T. Lin, Ph.D.
Review Chemist

Appendix A
(Labeling and Nomenclature Committee)

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT # 1007	HFD# 580	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION: DAVID T. LILN, Ph.D.		CENESTIN	Synthetic conjugated estrogens tablets

A. Look-alike/Sound-alike

Potential for confusion:

	Low	Medium	High
	Low	Medium	High
	Low	Medium	High
	Low	Medium	High
	Low	Medium	High

B. Misleading Aspects:

C. Other Concerns:

D. Established Name

_____ *Satisfactory*

_____ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE _____ UNACCEPTABLE

F. Signature of Chair/Date D W Boring 6/11/99

Appendix B
(EER)

06-NOV-1998

FDA CDER EES -
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 20992/000
Stamp: 30-MAR-1998
Regulatory Due: 30-MAR-1999
Applicant: DURAMED PHARMS
5040 LESTER RD
CINCINNATI, OH 45213
Priority: 3S
Org Code: 580

Action Goal:
District Goal: 28-NOV-1998
Brand Name: CENESTIN(SYNTHETIC CONJUGATED ESTROGENS)
Estab. Name:
Generic Name: SYNTHETIC CONJUGATED ESTROGENS TABS

Dosage Form: (TABLET)
Strength: SEE COMMENTS

Application Comment: THE TABLET STRENGTHS ARE: 0.3, 0.625, 0.9, 1.25, 2.5 MG. (on 04-MAY-1998 by D. LIN (HFD-580) 301-827-4230)

FDA Contacts:

D. MOORE	(HFD-580)	301-827-4236	Project Manager
D. LIN	(HFD-580)	301-827-4230	Review Chemist
M. RHEE	(HFD-580)	301-827-4237	Team Leader

Overall Recommendation:

Establishment: 1526814
DURAMED PHARMACEUTICALS INC
5040 LESTER RD
CINCINNATI, OH 45213

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
Profile: TCM OAI Status: NONE
Estab. Comment: DRUG PRODUCT MANUFACTURER. PERFORMS THE PACKAGING, RELEASE TESTING AND STABILITY TESTING OF THE DRUG PRODUCT TABLETS. (on 08-MAY-1998 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAY-1998				
SUBMITTED TO DO	11-MAY-1998	10D			LINDAV
ASSIGNED INSPECTION	18-MAY-1998	PS			DAMBROGIOJ
INSPECTION SCHEDULED	18-JUN-1998		30-JUN-1998		DGRELLE
INSPECTION PERFORMED	29-OCT-1998		21-OCT-1998		DGRELLE
					DGRELLE

Establishment:

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator

SUBMITTED TO OC	08-MAY-1998		
OC RECOMMENDATION	11-MAY-1998	ACCEPTABLE BASED ON PROFILE	LINDAV DAMBROGIOJ

Establishment:

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-OCT-1998				
OC RECOMMENDATION	29-OCT-1998			ACCEPTABLE BASED ON PROFILE	LINDAV FERGUSONS

Establishment:

BI
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAY-1998				
SUBMITTED TO DO	11-MAY-1998	GMP			LINDAV
ASSIGNED INSPECTION	14-MAY-1998	GMP			EGASM
INSPECTION SCHEDULED	22-JUL-1998		06-AUG-1998		EGASM
INSPECTION PERFORMED	25-AUG-1998		24-JUL-1998		EGASM
DO RECOMMENDATION	31-AUG-1998				DAMBROGIOJ
				WITHHOLD DRUG NOT MADE HERE	DAMBROGIOJ
EI OF 8/3-6/98 FOUND THIS SITE NOT DOING FUNCTION. FUNCTION BEING PERFORMED AT SITE IN MEXICO.					
OC RECOMMENDATION	31-AUG-1998				
				WITHHOLD FACILITY NOT DOING FUNCTION	DAMBROGIOJ

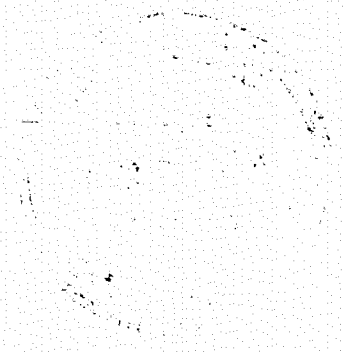
Establishment:

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment:

06-NOV-1998

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAY-1998				LINDAV
SUBMITTED TO DO	11-MAY-1998	GMP			EGASM
ASSIGNED INSPECTION	14-MAY-1998	GMP			EGASM
INSPECTION SCHEDULED	22-JUL-1998		30-JUL-1998		EGASM
INSPECTION PERFORMED	04-AUG-1998		31-JUL-1998		EGASM
DO RECOMMENDATION	23-SEP-1998			ACCEPTABLE	DAMBROGIOJ
OC RECOMMENDATION	23-SEP-1998			INSPECTION ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ



D Moore

FEB - 1 1999

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580
Review of Chemistry, Manufacturing and Controls

NDA #: 20-992
CHEMISTRY REVIEW #: 2 **DATE REVIEWED:** 29-JAN-1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	30-MAR-98	30-MAR-98	03-APR-98
Amendment	09-DEC-98	10-DEC-98	
Amendment	15-DEC-98	16-DEC-98	

NAME & ADDRESS OF SPONSOR: Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, OH 45213

DRUG PRODUCT NAME:
Proprietary: Cenestin Tablets
Nonproprietary/Established/USAN: Synthetic conjugated estrogens Tablets
Code Name/#:
Chem.Type/Ther.Class: 3S

PARMACOLOGICAL CATEGORY/INDICATION: Estrogen/Treatment of Post Menopausal Vasomotor Symptoms
DOSAGE FORM: Tablet
STRENGTHS: 0.3, 0.625, 0.9, 1.25, 2.5 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: x Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
The active drug substance for this product is composed of a 9 component estrogen mixture:
See Chemistry Review #1 (11/19/98).

CONCLUSIONS & RECOMMENDATIONS:

This NDA is approvable pending satisfactory resolution of the drug product established name, and final review of the dissolution and content uniformity methods in the methods validation report.

cc:
Orig. NDA #20-992
HFD-580/Division File
HFD-580/DMoore
HFD-580/MRhee/DLin

R/D Init by: 2/1/99
filename: nda20992.2 (doc)

1/29/99
David T. Lin, Ph.D.
Review Chemist

15-DEC-1998 FDA CDER EES Page 1 of 3

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 20992/000
Stamp: 30-MAR-1998
Regulatory Due: 30-MAR-1999
Applicant: DURAMED PHARMS
5040 LESTER RD
CINCINNATI, OH 45213
Priority: 3S
Org Code: 580

Action Goal:
District Goal: 28-NOV-1998
Brand Name: CENESTIN(SYNTHETIC CONJUGATED ESTROGENS)
Estab. Name:
Generic Name: SYNTHETIC CONJUGATED ESTROGENS TABS

Dosage Form: (TABLET)
Strength: SEE COMMENTS

Application Comment: THE TABLET STRENGTHS ARE: 0.3, 0.625, 0.9, 1.25, 2.5 MG. (on 04-MAY-1998 by D. LIN (HFD-580) 301-827-4230)

FDA Contacts:

D. MOORE	(HFD-580)	301-827-4236	, Project Manager
D. LIN	(HFD-580)	301-827-4230	, Review Chemist
M. RHEE	(HFD-580)	301-827-4237	, Team Leader

Overall Recommendation: ACCEPTABLE on 18-NOV-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 1526814
DURAMED PHARMACEUTICALS INC
5040 LESTER RD
CINCINNATI, OH 45213

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: TCM OAI Status: NONE

Estab. Comment: DRUG PRODUCT MANUFACTURER. PERFORMS THE PACKAGING, RELEASE TESTING AND STABILITY TESTING OF THE DRUG PRODUCT TABLETS. (on 08-MAY-1998 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAY-1998				LINDAV
SUBMITTED TO DO	11-MAY-1998	10D			DAMBROGIOJ
ASSIGNED INSPECTION	18-MAY-1998	PS			DGRELLE
INSPECTION SCHEDULED	18-JUN-1998		30-JUN-1998		DGRELLE
INSPECTION PERFORMED	29-OCT-1998		21-OCT-1998		DGRELLE
DO RECOMMENDATION	18-NOV-1998			ACCEPTABLE ADEQUATE FIRM RESPONSE INSPECTION	DGRELLE
OC RECOMMENDATION	18-NOV-1998			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

DURAMED SUBMITTED A WRITTEN RESPONSE TO THE FDA-483 AND ADDRESSED SOME FOLLOW-UP QUESTIONS. ALL ISSUES HAVE BEEN ADDRESSED AND WE HAVE NO FURTHER CONCERNS AT THIS TIME.

Establishment

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAY-1998				LINDAV
OC RECOMMENDATION	11-MAY-1998			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment:

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-OCT-1998				LINDAV
OC RECOMMENDATION	29-OCT-1998			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment:

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAY-1998				LINDAV
SUBMITTED TO DO	11-MAY-1998	GMP			EGASM
ASSIGNED INSPECTION	14-MAY-1998	GMP			EGASM
INSPECTION SCHEDULED	22-JUL-1998		06-AUG-1998		EGASM
INSPECTION PERFORMED	25-AUG-1998		24-JUL-1998		DAMBROGIOJ
DO RECOMMENDATION	31-AUG-1998			WITHHOLD	DAMBROGIOJ
OC RECOMMENDATION	31-AUG-1998			WITHHOLD FACILITY NOT DOING FUNCTION	DAMBROGIOJ

Establishment:

15-DEC-1998

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAY-1998				LINDAV
SUBMITTED TO DO	11-MAY-1998	GMP			EGASM
ASSIGNED INSPECTION	14-MAY-1998	GMP			EGASM
INSPECTION SCHEDULED	22-JUL-1998		30-JUL-1998		EGASM
INSPECTION PERFORMED	04-AUG-1998		31-JUL-1998		EGASM
DO RECOMMENDATION	23-SEP-1998			ACCEPTABLE	DAMBROGIOJ
OC RECOMMENDATION	23-SEP-1998			INSPECTION ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-992

PHARMACOLOGY REVIEW(S)

Review and Evaluation of Pharmacology/Toxicology Data

HFD-580/Alex Jordan, PhD

NDA 20-992

Sponsor: Duramed Pharmaceuticals, Inc

Submission: March 27, 1998

Cenestin (Synthetic Conjugated Estrogens) Tablets

Indication: Treatment of postmenopausal symptoms

2/23/99

Alex Jordan, PhD

NDA 20-992
HFD-580
AJordan

Duramed has submitted a 505(b)(2) application for a drug product Cenestin, containing 9 estrogenic compounds. Because of the vast clinical experience with conjugated estrogens and estrogens in general, and the published literature on conjugated estrogen toxicology (particularly carcinogenicity) in experimental animals, the Duramed application contains no Pharmacology/Toxicology information.

There is extensive literature on the function and activities of action of estrogens in humans and in numerous animal models. These studies have examined the mechanism of action of estrogens, their binding to estrogen receptors, activation of estrogen response elements, metabolism, pharmacokinetics and relative potencies. Conjugated estrogens and estrogens in general have been the subject of substantial toxicological evaluation (Westerholm, Pharmacol. Ther. 10:337-349. 1980; Hart, Pharmacol.Ther. 47:203-218, 1990). Additional toxicology studies comparing the toxicity of different preparations of conjugated estrogens are not necessary. Current toxicology studies attempt to identify all potential toxicities of a particular drug. To this end, high doses are used to overcome the inherent weakness of small numbers of animals and the differences in sensitivity between animals and humans. Only major toxicity differences would be expected to be revealed with these tests. Studies designed to differentiate small or subtle differences between two drug products are not feasible and have not been requested by the Center. The general applicability of any small differences observed in preclinical studies to the clinical use would be questionable. In addition, there are significant concerns about the predictive value of toxicology findings in other species for estrogen toxicity in humans (Hart, Pharmacol. Ther. 47:203-218, 1990).

One of the principal preclinical testing requirements for a drug used chronically is a carcinogenicity study. The issue of potential carcinogenicity has been addressed for conjugated estrogens. In June of 1998, the International Agency for Research on Cancer (IARC) met in Lyon, France to consider the carcinogenicity of postmenopausal estrogen therapies along with steroidal contraceptives. After considering all the published data in animals and humans, IARC stated that there is sufficient evidence in humans for the carcinogenicity of postmenopausal estrogen therapy. They went on to state that there is sufficient evidence in experimental animals for the carcinogenicity of 17 beta-estradiol and estrone and that there is limited evidence in experimental animals for the carcinogenicity of conjugated estrogens, equilin and estriol.

The evidence for carcinogenicity of conjugated estrogens came from two papers of studies in Hamsters with hydrolyzed Premarin, equilin and d-equilenin, and estrone (Li, et.al., Cancer Res. 1983; Li, et.al., Cancer Res. 1995). In these studies, there was a positive but limited correlation between estrogenicity and tumorigenicity. Estrone, equilin + d-equilenin, and Premarin produced tumors in 100% of the animals. In a separate study, equilin alone gave a 75% response and d-equilenin alone gave a 0% response. Thus, from a toxicologic perspective, the carcinogenic potential of these component estrogens has already been determined and further animal testing of the components would not likely change the estimation of human health risk.

Conclusion: Any difference in toxicity between the approved estrogen products and Cenestin would be expected to be small and subtle. No current animal toxicology studies have the power to detect such differences, if they exist, and the applicability of any small measured differences from such preclinical testing would be questionable. It is concluded that additional toxicology studies are not needed nor appropriate to support the safety of Cenestin.

Recommendation: Pharmacology recommends approval of Cenestin for the treatment of postmenopausal symptoms.

Labeling: The label conforms to the labeling guidance for estrogen drug products and is satisfactory.

Westerholm, B. Clinical toxicology of estrogens. Pharmacol. Ther. 10:337-349 (1980).

Hart, J.E. Endocrine pathology of estrogens: species differences. Pharmacol. Ther. 47:203-218 (1990).

Li, J.J., Li, S.A., Klicka, J.K., Parsons, J.A., and Lam L.K.T. Relative Carcinogenic Activity of Various Synthetic and Natural Estrogens in the Syrian Hamster Kidney. Cancer Research 43:5200-5205, 1983.

Li, J.J., Li, S.A., Oberley, T.D., and Parsons, J.A. Carcinogenic Activities of Various Steroidal and Nonsteroidal Estrogens in the Hamster Kidney: Relation to Hormonal Activity and Cell Proliferation. Cancer Research 55:4347-4351, 1995.