

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-443

Administrative/Correspondence

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-443	Efficacy Supplement Type SE-	Supplement Number
Drug: Enjuvia		Applicant: Barr Research, Inc.
RPM: George Lyght		HFD- 580 Phone # 301-827-4260
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		May10, 2004
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
● User Fee Information		
• User Fee		<input type="checkbox"/> Paid
• User Fee waiver (Original submission was done by a small business company-Endeavor)		<input checked="" type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified
❖ Exclusivity Summary (approvals only)		
● Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		

General Information	
● Actions	
• Proposed action	(x) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	Approvable
• Status of advertising (approvals only)	() Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (x) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(x) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	None
• Documentation of discussions and/or agreements relating to post-marketing commitments	NA
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	January 22, 2002
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	
Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	May 5, 2004
❖ Clinical review(s) (indicate date for each review)	May 5, 2004
● Microbiology (efficacy) review(s) (indicate date for each review)	
● Safety Update review(s) (indicate date or location if incorporated in another review)	In clinical review
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	x
❖ Statistical review(s) (indicate date for each review)	In clinical review
❖ Biopharmaceutical review(s) (indicate date for each review)	May 4, 2004
● Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	NA

❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	See clinical review
• Bioequivalence studies	See BioPharm review
CMC Information	
❖ CMC review(s) (indicate date for each review)	May 7, 2004
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	See CMC review
• Review & FONSI (indicate date of review)	See CMC review
• Review & Environmental Impact Statement (indicate date of each review)	See CMC review
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	
❖ Facilities inspection (provide EER report)	Date completed: February 11, 2003 (x) Acceptable () Withhold recommendation
❖ Methods validation	(x) Completed () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	January 22, 2003
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	
❖ CAC/ECAC report	

Appears This Way
On Original

Enjuvia™

Division Director's Addendum to Team Leader Memorandum

To: 21-443

From: Daniel Shames, MD
Director, HFD-580

Date: 5-21-04

Re: Enjuvia (synthetic conjugated estrogens, B) 0.625 and 1/25 mg tablets
Duramed Pharmaceuticals, Subsidiary of Barr Pharmaceuticals, Inc.

Background:

This application was approved on May 10, 2004. At that time, no documentation had been archived to address the combination drug policy as it relates to this drug product. The purpose of this memorandum is to remedy this lack of documentation.

Conclusion Regarding the Combination Drug Policy as it Relates to Enjuvia:

Under 21 CFR 300.50(c), fixed-combination prescription drugs for humans that have been determined to be effective for labeled indications by the FDA, based on evaluation of the NAS-NRC report of the combination, are considered to be in compliance with the requirements of the fixed-combination drug policy in 21 CFR 300.50.

The 1972 DESI findings for short-acting estrogens, including conjugated estrogens, are applicable to the combination of conjugated estrogens found in Enjuvia for the purposes of 21 CFR 300.50(c). Therefore, Enjuvia is considered to be in compliance with the requirements of the fixed-combination drug policy in 21 CFR 300.50.

This finding is consistent with that pertaining to previously approved conjugated estrogen products.

Appears This Way
On Original

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Margaret Kober
5/21/04 03:55:46 PM
CSO
Chief, Project Management Staff

Daniel A. Shames
5/28/04 11:15:53 AM
MEDICAL OFFICER

MEMO

To: Daniel Shames, MD
Director, Division of Reproductive and Urologic Drug Products
HFD-580

From: Kristina C. Arnwine, PharmD
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Through: Denise P. Toyer, PharmD
Team Leader, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Carol A. Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

CC: George Lyght, R.Ph.
Project Manager, Division of Reproductive and Urologic Drug Products
HFD-580

Date: April 16, 2004

Re: ODS Consult 02-0137-4, Enjuvia (Synthetic Conjugated Estrogens, B Tablets)
0.625 mg and 1.25 mg; NDA 21-443

This memorandum is in response to a March 31, 2004 request from your Division for a final review of the proprietary name, Enjuvia. The container labels and carton and insert labeling were provided for review and comment.

DMETS has not identified any additional proprietary names as having potential sound-alike and look-alike confusion with Enjuvia since we conducted our initial and follow-up reviews dated March 21, 2002, December 9, 2002, and January 21, 2004 that would render the name objectionable (see ODS Consults 02-0137, 02-0137-1, and 02-0137-3).

In the review of the Enjuvia container labels and carton labeling, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. Bottle Container Labels

1. The white font on the pink background color (0.625 mg strength) makes the milligram strength difficult to distinguish. Please revise the color scheme so that the expression of strength is easier to read.
2. Relocate the net quantity so that it does not appear in close proximity to the milligram strength.

B. Professional Sample Blister Cards

1. Add the statement, "each tablet contains 0.625 mg of synthetic conjugated estrogens, B."
2. Please include directions on how to remove the tablets from the blister card.
3. Please list the net quantity of tablets in each blister card.

In summary, DMETS does not have any objections to the use of the proprietary name Enjuvia. Additionally, DDMAC finds the proprietary name Enjuvia acceptable from a promotional perspective. DMETS recommends implementation of the label and labeling revisions outlined above. DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Sammie Beam at 301-827-2102.

**Appears This Way
On Original**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Kristina Arnwine
4/23/04 01:52:28 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
4/26/04 12:32:31 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
4/26/04 04:08:58 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 25, 2002

TO: Daniel Shames, M.D., Director
Division of Reproductive and Urologic Drug Products
HFD-580

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Regulatory Health Project Manager
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Anne Trontell, M.D., M.P.H., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for Enjuvia™,
NDA 21- 443

The patient labeling which follows represents the revised risk communication materials for Enjuvia™, NDA 21- 443. It has been reviewed by our office and by DDMAC. We have simplified the wording, made it consistent with the PI, removed promotional language and other unnecessary information and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

Comments to the review division are bolded, italicized, and underlined. Please call us if you have any questions.

5 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Jeanine Best
11/25/02 03:36:31 PM
CSO

Toni, Please sign for Anne.

Toni Piazza Hepp
11/26/02 09:49:57 AM
PHARMACIST
for Anne Trontell



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 57,111

Endeavor Pharmaceuticals
Attention: John West
Director, Regulatory Affairs
127 Racine Drive, Suite 202
Wilmington, NC 28403

Dear Mr. West:

Please refer to your submission dated February 25, 2002, requesting a waiver for pediatric studies for Enjuvia (synthetic 10-component conjugated estrogens) tablets.

We have reviewed the submission and agree that a full waiver is justified for Enjuvia for the indication "treatment of moderate-to-severe vasomotor symptoms associated with the menopause" because the indication does not exist in children, the product is not likely to be used in a substantial number of pediatric patients, and the product does not represent a meaningful therapeutic benefit for pediatric patients over existing treatments.

Accordingly, a full waiver for pediatric studies for your application for moderate-to-severe vasomotor symptoms associated with the menopause is granted under 21 CFR 314.55 at this time.

Should you anticipate submitting an application for a treatment of vulvar and vaginal atrophy indication in the future, please submit additional information regarding that indication in pediatric patients. Alternatively, a request for a pediatric waiver for that indication, along with your justification for a waiver, can be submitted for review.

You are referred to the Division of Metabolic and Endocrine Drug Products (HFD-510) regarding any future request for a waiver for pediatric studies for a prevention of postmenopausal osteoporosis indication.

IND 52,771
Page 2

If you have any questions, call Diane Moore, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Acting Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Daniel A. Shames
3/18/02 04:43:01 PM

IND 57,111

Pre-NDA pre meeting notes

January 22, 2002

Page 2

Discussion Items:

- the sponsor has submitted the terms [] and [] to USAN for comment for the established name
- the sponsor proposes to submit the NDA application as a 505 (b) (2) submission; literature references for pharmacology will be submitted
- a Drug Master File (DMF) by [] will be referenced in the NDA submission for the drug substance
- [] is not being pursued; the sponsor is seeking [] expiration for the product
- the [] facility will be the primary manufacturer for the to-be-marketed drug product; one lot of each strength was manufactured at [] no over-encapsulation of the product was made for the clinical study batches; a subset of registration lots were made at [] for use in linking the two manufacturing sites; samples for release and stability testing were manufactured at [] as bulk
- the tablet batches used in the pivotal clinical trial are the same composition as the registration batches except for the added color coating
- [] registration batches were manufactured (three at [] the clinical batches were a subset of the three registration batches made at [] the clinical lots made at [] were not used in the VMS trial but were used in the osteoporosis trials; no VMS data was obtained in the osteoporosis study

Decisions Reached:

- the established name for this substance would be "synthetic conjugated estrogens, B"; the established name, [] was discussed with USP; the Agency has precedence for this type of format for consistency (e.g., cyclodextran-type products, interferon products)

CMC Questions:

- **Question 1:** What sections of the NDA are preferred for presentation in electronic format?
- FDA response:
 - All sections in the CMC section can be submitted in electronic format; the format must conform to the current FDA guidance entitled, "Regulatory Submissions in Electronic Format, New Drug Applications" dated January 27, 1999; electronic format includes PDF, not Excel; a paper submission is also acceptable
- **Question 2:** Does the FDA agree with the proposal to support the NDA with the following stability package?
 - [] stability data on one lot for each of the [] 0.625 mg, and 1.25 mg NDA registration batches
 - [] stability data for two lots for each of the [] 0.625 mg, and 1.25 mg NDA registration batches
 - supportive data from [] batches consisting of:
 - [] data from one batch of each of the [] 0.625 mg, and 1.25 mg tablet strengths
 - [] data from one batch each of the [] and 0.625 mg batches
 - []
- FDA response:
 - the proposal is acceptable with the following comments:
 - the sponsor should refer to the guidance entitled, "Stability Testing of Drug Substances and Drug Products" (June 8, 1998) on the FDA web-page
 - updated stability data should be provided during the review cycle

- the use of [] batches is relevant as long as the batch size is at least [] of the commercial batch size
- []
- data should be provided on tablets packaged in all the proposed packaging configurations

• **Question 3:** Is the proposal to [] on the basis of the dissolution profile presented in the briefing package, relative to the dissolution profiles for the [] 0.625 mg strengths, acceptable?

• **Discussion:**

- []

•

•

• **FDA response:**

•

•

•

•

•

•

• **Question 4:** For purposes of measuring equilin sulfate dissolution levels, is the method outlined in paragraph 4 of the briefing package (dated Dec 20, 2001) page 12 acceptable?

• **Discussion:**

- the sponsor used []

- the sponsor claims that the proposed method are equal from lot-to-lot
- the sponsor proposed a lower limit of quantitation of [] for the Estrogenic Substances Assay for the finished product specifications (see overheads)
- **FDA response:**
 - in the methods section of the NDA, the proposed [] limit of quantitation appears to be acceptable
 - the Division noted that when the FDA laboratory in St. Louis separated conjugated estrogens using a HPLC/mass spectrophotometry method, []
 - the sponsor should submit data to support their assay methodology and clarify why the proposed method [] ; the report to be submitted for the dissolution analysis and should demonstrate that the dissolution profiles of the [] components are equivalent
 - typically, the Agency requires that all ten components of a product be monitored; in the case of conjugated estrogens, a compromise was made []
 - we recommend that the sponsor return to the method proposed in the 10/5/01 IND amendment
 - because HPMC is a control-release excipient, the sponsor should analyze the cores and present their justification to support the argument that the cores are the same for the different dosage strength tablets; the data should be submitted for discussion at the teleconference scheduled for February 21, 2002
 - the following data should be included in the NDA:
 - data to support a change in manufacturer
 - *in vitro* dissolution data comparing the clinical batches with the to-be-marketed batches
 - dissolution data comparing the white tablets and the colored tablets for linkage
- **Question 5:** Is it acceptable to [] manufacturing process for the drug product to [] after process validation is complete?
 - **FDA response:**
 - in-process testing is a surrogate for end-process testing; the proposed change should be made post-approval in a prior approval supplement
 - the sponsor should submit adequate data demonstrating that this change will not adversely affect the quality of the drug product
 - the submission should comply with the ICH Q6A agreement
- **Question 6:** Given the split between the pre-NDA meetings for the non-clinical and clinical related issues, does the Agency agree with a proposal to progress the NDA with a pre-submission of chemistry, manufacturing, and controls information? Such a package would consist of:
 - [] stability data on one lot for each of the [] 0.625 mg, and 1.25 mg NDA registration batches
 - [] stability data for two lots for each of the [] 0.625 mg, and 1.25 mg NDA registration batches
 - a commitment to provide [] stability data from these additional two NDA registration batches for each of the aforementioned tablet strengths at the time the remaining (e.g., clinical) components of the NDA are submitted

IND 57,111

Pre-NDA pre meeting notes

January 22, 2002

Page 5

- supportive data from [] batches consisting of:
 - [] data from one batch of each of the [] 0.625 mg, and 1.25 mg tablet strengths
 - [] data from one batch each of the [] 0.625 mg batches
 - []
- **FDA response:**
 - the proposal to pre-submit CMC data is acceptable
 - the PDUFA clock for the NDA would not start until the complete NDA is submitted
- Chemistry Points to Consider Prior to NDA Submission:
 - drug substance and drug product identification (ID) test should contain relative retention time for all ten components
 - for the synthetic conjugated estrogens products, all of the ten listed components need to be in the drug substance and each component needs to be in the percentage amount set by the lower and upper limits for that component
 - the drug product assay is based on []
 - [] with an acceptance criteria of [] of label claim
 - the term ' [] ' is not acceptable; the drug product specification [] should be combined with the "Assay" specification
 - the drug product assay specification should include the following with proposed numerical ranges:
 - Total of sodium estrone sulfate, sodium equilin sulfate and sodium 17 α -dehydroequilin sulfate
 - Sodium estrone sulfate
 - Sodium equilin sulfate
 - Sodium 17 α -dihydroequilin sulfate
 - Ratio of sodium equiline sulfate to sodium estrone sulfate
 - Sodium 17 β -dihydroequilin sulfate
 - Sodium 17 α -estradiol sulfate
 - Sodium 17 β -estradiol sulfate
 - Sodium equilenin sulfate
 - Sodium 17 α -dihydroequilenin sulfate
 - Sodium 17 β -dihydroequilenin sulfate
 - the drug product specifications should include tests for — and unidentified impurities/degradants on stability; ICH guidelines should be followed regarding unidentified impurities; justification should be submitted for not including — testing
 - methods validation package should include a list of samples to be provided to lab, drug product composition, description of analytical methods, method validation data, material safety data sheet (MSDS)
- Biopharmaceutics Comments:
 - in the PK study ENDV-01-002 submitted to the sponsor's ANDA, a nine-component material was studied for food-effect; if the sponsor seeks to utilize data from that study to determine the food effects, bridging data would be required to link the data to the ten-component product; it should also be determined whether the tenth component would affect the pharmacokinetics of the measurable components of the ten-component product
 - the sponsor should provide arguments to the IND for linking the data from the food-effect study to the ten-component product prior to the meeting scheduled for February 21, 2002; study reports can be submitted to the NDA

IND 57,111
Pre-NDA pre meeting notes
January 22, 2002
Page 6

Action Items:

- | Item: | Responsible Person: | Due Date: |
|--|----------------------------|---------------------------|
| • minutes to sponsor | Ms. Moore | one month |
| • submit report of additional data supporting | Endeavor Pharmaceuticals | prior to February meeting |
| • submit information regarding release characteristics | Endeavor Pharmaceuticals | prior to February meeting |
| • submit information linking the 9-component product with the 10-component product | Endeavor Pharmaceuticals | prior to February meeting |

{See appended electronic signature page}

{See appended electronic signature page}

Signature, recorder

Signature, Chair

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

drafted: dm/121602/157111PM121602.doc

Concurrence:

B.Gierhart 1.29.02/S.De 1.30.02/S.Slaughter 2.1.02/D.Lin 2.5.02/V.Jarugula 2.5.02
Responses not received from L.Stephens, E.Duffy

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Diane V. Moore
2/8/02 04:17:42 PM

David T. Lin
2/8/02 04:47:03 PM
I concur.

Lin

MEETING MINUTES

Date: June 19, 1998 Time: 2:00 p.m.- 3:30 p.m. Location: Parklawn 17B-43

IND: PRE-IND Drug Name: Low-Dose Conjugated Estrogen

Type of Meeting: Pre-IND Industry

Meeting Chair: Dr. Lisa Rarick

Meeting Recorders: Mr. John C. Markow

FDA Attendees:

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products
DRUDP (HFD-580)

Marianne Mann, M.D., - Deputy Director, Division of Reproductive and Urologic Drug
Products (DRUDP;HFD-580)

Theresa van der Vlugt, M.D. - Medical Officer, DRUDP (HFD-580)

John Gibbs, Ph.D. - Division Director, Division of New Drug Chemistry II (DNDC II)

Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, (DNDC II) @ DRUDP (HFD-580)

David Lin, Ph.D. - Chemist, (DNDC II) @ DRUDP (HFD-580)

Angelica Dorantes, Ph.D. - Pharmacokinetic Team Leader, Division of Pharmaceutical
Evaluation II (DPE II) @ DRUDP (HFD-580)

Kate Meaker, M.S. - Mathematical Statistician, Division of Biometrics II (DBII) @ DRUDP
(HFD-580)

John C. Markow, R.Ph., J.D. - Project Manager, DRUDP (HFD-580)

External Attendees:

Frederick Sancilio, Ph.D., - President and CEO

Kenneth Lomartire, - Executive Vice President, Worldwide R&D

James Swarbrick, D.Sc., Ph.D., Vice President, R&D

Christopher Smith, RAC, CQE - Vice President, Worldwide QA

James Lyon, Pharm D., - Director Pharmacokinetics

Edgar Fenzl, M.D., Ph.D., - Executive Vice President, Clinical Operations

Lois Q. Semmens, - Director, Regulatory Affairs

Robert Whittle, Ph.D., - Senior Scientist, CE Chemistry Expert

Meeting Objectives:

To discuss the submission of an IND for low-dose Conjugated Estrogens.

Background:

will be discussing an overall clinical and development plan for conjugated Estrogens along
with a plan for conducting a trial to evaluate the use of a Synthetic Ten Component Conjugated

Estrogen product for the indication of Vasomotor Symptoms.

Discussion Points:

CMC

1. Will less than the minimum ICH stability requirements be acceptable before submission of an NDA?

Ans.

No. Because this is a new formulation stability requirements according to ICH guidelines should be strictly adhered to before the submission of an NDA.

Pharmacology and Toxicology.

1. Will additional Pharm Tox studies be required?

Ans.

This application, if submitted as a 505 (b)(2) application would not require additional Pharm Tox studies.

Clinical

1. General issues

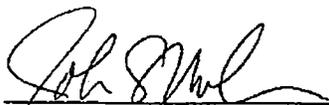
- to support a vasomotor symptoms indication, a single, adequate, placebo-controlled study would be required
- the number of hot flushes will be the primary criteria
- the active control arm of the proposed study would not be required
- the single study should assess the lowest effective dose of the study drug
- foreign data is acceptable

2. Inclusion and Exclusion Criteria

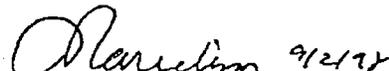
- patients included in the study do not need to have an intact uterus
- screening criteria should be changed to FSH > 40 mIU/ml and estradiol < 20 pg/ml
- patients with 12 months of spontaneous amenorrhea do not need to meet the FSH and estradiol criteria
- a decrease in the washout period to 4 weeks from 8 weeks is acceptable but not recommended

Statistics

- 30 patients per arm will likely not be enough to support one adequate study for VMS
- power calculations and sample size calculations should be provided if a single, placebo-controlled study is to be pursued



Signature, minutes preparer



Concurrence, Chair

drafted: jm/October 7, 1997/wordfile/ind/preind

cc: Original
HFD-580
HFD-580/
HFD-580/JMercier/LPauls/attendees

Concurrences:

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Diane V. Moore
3/22/02 05:07:41 PM