

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-609

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY FOR NDA # 21-609 SUPPL # _____

Trade Name Enjuvia Generic Name Synthetic conjugated estrogens, B

Applicant Name Duramed Pharmaceuticals, a subsidiary of Barr Laboratories, Inc. HFD-580 _____

Approval Date If Known December 20, 2004

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES / / NO / /

If yes, what type? Specify 505(b)1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505 (b) 1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_x_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_x_/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

NA

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_x_/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_x_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _004782 (Premarin) _____

NDA# _20992 (Cenestin) _____

NDA# __21-443 (Enjuvia) _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ___ / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# ___NA_____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to

question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_x_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_x_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_x_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_x_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_x_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study GA326

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_x_/

Investigation #1 !
 IND # 57,111_ YES /_x_/ ! NO /___/ Explain: _____
 !
 !

Investigation #2 !
 IND # _____ YES /___/ ! NO /___/ Explain: _____
 !

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
 YES /___/ Explain _____ ! NO /___/ Explain _____
 !
 _____ ! _____
 !
 _____ ! _____
 !

Investigation #2 !
 YES /___/ Explain _____ ! NO /___/ Explain _____
 !
 _____ ! _____
 !
 _____ ! _____
 !

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_x_/

If yes, explain: _____

Signature Kassandra Sherrod, R.Ph. Date: December 7, 2004
 Title: Regulatory Project

Manager

Signature of Office/
Division Director

Date

Form OGD-011347 Revised 05/10/2004

**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
12/20/04 02:15:58 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA:# 21-609 _____ Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: June 30, 2004 Action Date: December 20, 2004

HFD 580 Trade and generic names/dosage form: Enjovia (synthetic conjugated estrogens, B) Tablets

Applicant: Barr Research, Inc. Therapeutic Class: estrogens

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of moderate to severe vasomotor symptoms associated with menopause

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Adult studies ready for approval

Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-609
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

**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/

Kassandra C. Sherrod
12/20/04 12:05:49 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-609	Efficacy Supplement Type SE-	Supplement Number
Drug: Enjuvia (synthetic conjugated estrogens, B)		Applicant: Barr Research, Inc.
RPM: Kassandra Sherrod		HFD-580 Phone # 301-827-4260
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority • Chem class (NDAs only) • Other (e.g., orphan, OTC) 		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<input checked="" type="checkbox"/> ❖ User Fee Goal Dates		December 30, 2004
<input checked="" type="checkbox"/> ❖ 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 <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee 		<input type="checkbox"/> Paid UF ID number
<ul style="list-style-type: none"> • User Fee waiver 		<input checked="" type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
<ul style="list-style-type: none"> • User Fee exception 		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
<input checked="" type="checkbox"/> ❖ Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP 		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)

- Exclusivity summary
- Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)
- Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.

Yes, Application # _____
 No

❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)

↳ was there any in the 1st cycle → everything from 1st should be in here too.

General Information		
✓	❖ Actions <ul style="list-style-type: none"> • Proposed action • Previous actions (specify type and date for each action taken) • Status of advertising (approvals only) 	(×) AP () TA () AE () NA NA April 22, 2003 (×) Materials requested in AP letter () Reviewed for Subpart H
X	❖ Public communications <ul style="list-style-type: none"> • Press Office notified of action (approval only) • Indicate what types (if any) of information dissemination are anticipated 	() Yes (×) Not applicable (×) None () Press Release () Talk Paper () Dear Health Care Professional Letter
?	❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)) <ul style="list-style-type: none"> • 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, DMETS, DSRCS) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>) • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
	❖ Labels (immediate container & carton labels) <ul style="list-style-type: none"> • Division proposed (only if generated after latest applicant submission) • Applicant proposed • Reviews 	
X	❖ Post-marketing commitments <ul style="list-style-type: none"> • Agency request for post-marketing commitments • Documentation of discussions and/or agreements relating to post-marketing commitments 	
	❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
✓	❖ Memoranda and Telecons	
✓	❖ Minutes of Meetings <ul style="list-style-type: none"> • EOP2 meeting (indicate date) • Pre-NDA meeting (indicate date) • Pre-Approval Safety Conference (indicate date; approvals only) • Other 	
X	❖ Advisory Committee Meeting <ul style="list-style-type: none"> • Date of Meeting • 48-hour alert 	
X	❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

Summary Application Review

✓ ❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	
---	--

Clinical Information

✓ ❖ Clinical review(s) <i>(indicate date for each review)</i>	
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	
❖ Risk Management Plan review(s) <i>(indicate date/location if incorporated in another rev)</i>	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	
❖ Demographic Worksheet <i>(NME approvals only)</i>	
❖ Statistical review(s) <i>(indicate date for each review)</i>	
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	

CMC Information

❖ CMC review(s) <i>(indicate date for each review)</i>	
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	
• Review & FONSI <i>(indicate date of review)</i>	
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Microbiology (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	
❖ Facilities inspection (provide EER report)	Date completed: () Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested () Not yet requested

Nonclinical Pharm/Tox Information

❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	
❖ CAC/ECAC report	

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

MEMORANDUM OF TELECON

DATE: July 22, 2003

APPLICATION NUMBER: NDAs 21-443 & 21-609

Enjuvia (synthetic conjugated estrogens, B) tablets

BETWEEN:

Name: Christopher Smith, Vice President, Regulatory Affairs and Quality Assurance

Phone: (910) 200-3089

Representing: Endeavor Pharmaceuticals, Inc.

AND

Name: Margaret Kober, R.Ph., Chief, Project Management Staff
Daniel Shames, M.D., Director

Division of Reproductive and Urologic Drug Products, (DRUDP)
HFD-580

SUBJECT: efficacy standards for drug products to treat postmenopausal symptoms and steps forward for the Enjuvia applications

Endeavor had provided Dr. Shames with a re-analysis of the efficacy data for Enjuvia to help in his preparation for a meeting with senior management. Although the Center director was unexpectedly unable to attend, the meeting resulted in a number of decisions.

Therefore, Endeavor was encouraged to formally submit the re-analysis as a complete response to the Not Approvable letter for NDA 21-609. This submission will be given a 6-month clock. A complete response to the Approvable letter for NDA 21-443 should be submitted 4 months after the complete response to NDA 21-609. The second submission will be on a 2-month clock. This will facilitate simultaneous actions on all proposed strengths.

Daniel Shames, M.D.
Director

**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
8/20/03 09:52:24 AM
CSO
Signed for Daniel Shames

Internal Meeting Minutes

Date: July 29, 2004 Time: 10:00 - 11:00 AM Place: Parklawn, Room 17B-43

NDA: 21-609 Drug Name: Enjuvia™ (synthetic conjugated estrogens, B)
Tablets 0.3 mg and 0.45 mg

Type of Meeting: Complete Response/Status meeting

Indication: Treatment of moderate to severe vasomotor symptoms associated with the menopause

Sponsor: Barr Research, Inc.

FDA Lead: Brenda Gierhart, M.D.

Meeting Recorder: Charlene Williamson

FDA Participants:

Brenda Gierhart, M.D., Team Leader, Division of Reproductive and Urologic Drug Products
DRUDP (HFD-580)

Bruce Patsner, M.D., Medical Officer, DRUDP (HFD-580)

Charlene Williamson, Project Manager, DRUDP (HFD-580)

Moh-Jee Ng, M.S., Statistician, Division of Biometrics II (DBII; HFD-715)

Mike Welch, Ph.D., Biostatistics Team Leader

Meeting Objective:

To discuss the acceptance of the sponsor's June 29, 2004, response to our Not Approvable letter dated April 22, 2003 for the 0.3 mg and 0.45 mg strengths of Enjuvia™ for the treatment of moderate to severe vasomotor symptoms associated with the menopause.

Background:

Endeavor, the original sponsor of the NDA was issued a not approvable letter dated April 22, 2003. A complete response was submitted on August 29, 2003 to the not approvable letter and accepted by the division. On January 29, 2004, the August 29, 2003 submission was withdrawn. Barr Research, the current sponsor of the NDA has submitted a response dated June 29, 2004. The 6-month User Fee Goal date is December 30, 2004.

Discussion:

Clinical

- Acceptable as a complete response.

Statistics

- DRUDP can accept their data as a complete response to their approval letter dated April 22, 2003.
- Statistician anticipates having their review completed by end of September

Action items:

Sponsor will be asked the following:

- Were the analyses submitted on June 29, 2004 performed on the data submitted in the original NDA or on revised data?
- How was the diary data missing from the data submitted in the original NDA handled in the June 29, 2004 analyses?
- Provide the original data sets.
- Submit a copy of the original Statistical Analysis Plan and all amendments.
- Provide SAS program that generated Tables 3-5 of "Amendment to a Pending Application Responses to the Not Approvable Letter" on June 29, 2004.
- Clarify how centers were pooled.

Signature, minutes preparer

Signature, Chair

cc:
HFD-580
NDA 21-609

Drafted: Sherrod, 8.4.04

Concurrence/Comments: Ng, 8.5.04/Patsner, 8.14.04/Gierhart, 8.25.04

Finalized: Sherrod, 8.31.04

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

/s/

Brenda Gierhart
9/1/04 10:31:09 AM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 21, 2003

TIME: 9:30 am – 11:00 pm

LOCATION: Parklawn Conference Room 13B-39

APPLICATION: NDA 21-443 and NDA 21-609

SPONSOR: Endeavor Pharmaceuticals

TYPE OF MEETING: Type A

MEETING CHAIR: Daniel Shames, M.D. Director
Division of Reproductive and Urologic Drug Products (DRUDP,
HFD-580)

MEETING RECORDER: George Lyght, R.Ph., Regulatory Project Manager

FDA ATTENDEES:

Shelley R. Slaughter, M.D. Ph.D., Team Leader DRUDP (HFD-580)
Phill H. Price, M.D. Medical Reviewer, DRUDP (HFD-580)
Theresa van der Vlugt, M.D., Medical Reviewer, DRUDP (HFD-580)
Katherine Meaker, MS., Statistics Reviewer, Reviewer, DRUDP (HFD-580)
Mike Welch, Ph.D., Statistics Team Leader, DRUDP (HFD-580)
Ameeta Parekh, Ph.D., Biopharmaceutics Team Leader, DRUDP (HFD-580)
Margaret Kober, R.Ph., Chief Project Management Staff, DRUDP (HFD-580)
Bronwyn Collier, Associate Director for Regulatory Affairs, ODE III
Moh-Jee Ng, MS. Statistics Reviewer, DRUDP (HFD-580)

EXTERNAL ATTENDEES:

R. Forrest Waldon, Present and Chief Executive Officer
Thomas W. Leonard, Ph.D., Vice President and Chief Scientific Officer
Christopher Smith, Vice President of Regulatory Affairs and Quality Assurance

Phillip M. Sarrel, M.D. Professor of Obstetrics and Gynecology and Psychiatry, Yale University
School of Medicine

James Simon, M.D. Clinical Professor of Obstetrics and Gynecology, George Washington
University School of Medicine

Wulf Utain, M.D., Ph.D. Executive Director North American Menopause Society, Professor
Emeritus of Reproductive Biology and Obstetrics and Gynecology, Case Western Reserve School
of Medicine

Meeting Objective:

To discuss the Sponsor's additional analysis of previously submitted clinical data for Enjuvia 0.3 mg tablets

Background:

Endeavor filed an NDA 21-443 seeking approval for Enjuvia™ (synthetic conjugated estrogens, B) 0.3 mg, 0.45 mg, 0.625 mg and 1.25 mg tablets. The indication was for the treatment of moderate to severe vasomotor symptoms associated with menopause. The Division issued a not-approvable letter on April 22, 2003 for Enjuvia 0.3 mg and 0.45 mg tablets, assigning these strengths a new NDA number NDA 21-609. A meeting was requested by Endeavor Pharmaceuticals to discuss the not-approvable action letter. The 0.625 mg and 1.25 mg tablets were the subject of an April 22, 2003 approvable letter based on lack of agreed upon labeling.

Discussion:

- The Sponsor provided a presentation on their study GA326 and a re-analysis of data to support approval.

FDA response

- DRUDP reiterated that the current position regarding approvability of Enjuvia 0.3 mg tablets stands.
- Post-hoc re-analysis after failure of primary endpoints is not an appropriate avenue to approval.
- Maintaining consistency among sponsors is an overriding issue

ACTION ITEMS:

- An appeal of the decision can be made to Dr. Houn 's office
- Meeting minutes to be conveyed to the sponsor within 30 days.

Minutes Preparer: _____

George Lyght, R.Ph.
Regulatory Project Manager

Chair Concurrence: _____

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

Endeavor Pharmaceuticals
May 21, 2003
Page 2

cc: Original
HFD-580 /Div. Files
HFD-580/Lyght
HFD-580/

Drafted by: gl/06.18.03
Initialed by: Welch/06.23.03/Kober/06.23.03/van der
Vlugt/06.23.03/Collier/06.23.03/Parekh/06.23.03
final: gl/07.02.03

MEETING MINUTES

**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
7/24/03 11:56:02 AM



NDA 21-609

Endeavor Pharmaceuticals
Attention: John West
127 Racine Drive
Wilmington, NC 28403

Dear Mr. West:

Please refer to your new drug application (NDA) dated March 21, 2002, received March 22, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Enjuvia™ (synthetic conjugated estrogens, B) 0.3 mg and 0.45 mg tablets.

We acknowledge receipt of your submissions dated May 2, 3, 17, June 21, 27, July 10, 17, August 30, September 27, October 4, 10, 23, November 18, December 5, 19, and 23, 2002, January 17, February 11, 12, 28, March 20, 24, 27, April 1, 7, and 21, 2003. These submissions were reviewed for this action.

We completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

1. Efficacy was not demonstrated for Enjuvia™ 0.3 mg tablets in the treatment of moderate to severe vasomotor symptoms associated with the menopause. For estrogen products intended to treat moderate to severe vasomotor symptoms, the division recommends that the primary efficacy analyses show a clinically and a statistically significant reduction, within 4 weeks of initiation of treatment and maintained throughout 12 weeks of treatment, in both the frequency and severity of hot flushes in the treated groups compared with the control groups. When comparing the subject group treated with Enjuvia™ 0.3 mg tablets to the group treated with placebo, a statistically significant reduction in both frequency and severity of moderate to severe vasomotor symptoms was not demonstrated until week 12 of treatment.
2. You sought to obtain approval for Enjuvia™ 0.45 mg for the treatment of moderate to severe vasomotor symptoms by bracketing the 0.45mg dosage strength between the 0.3 mg tablet and the 0.625 mg tablet. Because the Enjuvia™ 0.3 mg dosage strength is not approvable, this indication can not be granted for Enjuvia™ 0.45 tablet.

To address the above deficiencies you may:

1. conduct a new vasomotor symptom clinical trial with results that demonstrate for both Enjuvia™ 0.3 and 0.45 mg tablets a clinically and statistically significant reduction in the frequency and

severity of hot flushes when compared with placebo. This reduction should occur by 4 weeks after initiation of treatment and should be maintained throughout 12 weeks of treatment.

2. alternatively obtain the indication for the treatment of moderate to severe vasomotor symptoms for Enjuvia™ 0.45 mg tablets by bracketing between the 0.3mg and 0.625mg dosage strengths if both the 0.3mg and 0.625 dosage strengths are approved for this indication.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact George Lyght, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
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
4/22/03 06:09:27 PM

MEMO

To: Daniel Shames, M.D.
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, Pharm.D.
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 Products
HFD-150

Date: January 21, 2004

Re: ODS Consult 02-0137-3, Enjuvia (synthetic conjugated estrogens, B tablets)
0.3 mg, 0.45 mg, 0.625 mg, and 1.25 mg; NDA 21-609

This memorandum is in response to a January 12, 2004 request from your Division for a final review of the proprietary name, Enjuvia. The insert labeling was provided for review and comment. However, container labels and carton labeling have not been reviewed by DMETS as of the date of this review.

The proposed proprietary name was found acceptable by DMETS on March 21, 2002 (ODS Consult 02-005). Since that review, DMETS has identified one additional proprietary name: Ejuva as having potential sound-alike and look-alike confusion with Enjuvia.

Ejuva is the proprietary name of an herbal intestinal cleansing program. The Ejuva Intestinal Cleansing Kit consists of five different herbal tablets and one shake. The tablets are called Power, Balance, Moflora, Renew, and Vibram which are all taken one to four times daily by mouth. The shake is called Combi Shake and is taken once daily by mouth. The intestinal cleansing program lasts up to four weeks. While Enjuvia and Ejuva do share both sound-alike and look-alike characteristics, the conditions of use are different.

Enjuvia is a prescription-only product which generally will only be prescribed to menopausal women. Enjuvia will be available in four different strengths, therefore a prescribing dose will be need to be included in a prescription. Enjuvia can be dispensed on both an inpatient and outpatient basis. Ejuva, an herbal supplement, is available without a prescription. According to an Ejuva representative, Ejuva is only available on the internet and through distributors such as raw foods stores, not at commonly found nutritional stores such as General Nutrition Center (GNC) or the Vitamin Shoppe. Therefore, the conditions of use will help to decrease the potential of medication errors between Enjuvia and Ejuva.

In summary, DMETS has no objection to the use of the proprietary name, Enjuvia. DDMAC finds the proprietary name acceptable from a promotional perspective.

We consider this a final review. If the approval of the NDA is delayed beyond 90 days from the date of this review, the name with its associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.

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 301-827-3242.

**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
2/3/04 03:04:21 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
2/3/04 03:08:13 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
2/4/04 07:11:04 AM
DRUG SAFETY OFFICE REVIEWER

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS Endeavor Pharmaceuticals, Inc. 127 Racine Drive, Suite 202 Wilmington, NC 28403	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 21-443
2. TELEPHONE NUMBER (Include Area Code) (910) 790-9811	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA).
3. PRODUCT NAME ENJUVIA™ Tablets	6. USER FEE I.D. NUMBER 4216

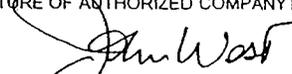
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CDER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 and 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
--	--	--

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Director, Regulatory Affairs	DATE 3/21/02
---	---------------------------------------	-----------------