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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-443

Medical Review(s)

NDA 21-443

Medical Officer's Review of NDA Amendment

Sponsor: Barr Research, Inc.
One Bala Plaza Suite 324
Bala Cynwyd, PA 19004-1401

Drug Name:
Generic: Synthetic conjugated estrogens, B
Trade: Enjuvia®

Pharmacologic category: Estrogen

Dosage form: Oral tablet

Strengths: 0.625 mg, 1.25 mg

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

Related submission: Primary Medical Officer review of NDA 21-443
March 28, 2003 by Brenda S. Gierhart, M.D

Date: May 3, 2004

I Recommendations

Approvability

This reviewer finds that the 0.625 mg and 1.25 mg Enjuvia™ (synthetic conjugated estrogens, B) tablets for treatment of moderate to severe vasomotor symptoms (VMS) associated with the menopause should be approved.

The original review of this NDA was conducted by Brenda Gierhart, M.D. and written on March 28, 2003. In that review Dr. Gierhart recommended that from a clinical point of view Enjuvia™ 0.625 mg and 1.25 mg tablets be approved pending satisfactory labeling negotiations with the Sponsor.

The basis for recommending approval pending satisfactory labeling changes was a demonstration that the product met the four primary efficacy endpoints (reduction in frequency and severity of moderate to severe VMS associated with the menopause from baseline to weeks 4 and 12) as described in the Agency's January 2003 Guidance for Industry document "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation." Clinical efficacy was demonstrated in Protocol GA-326; no new clinical data have been submitted nor are required for approval. A comprehensive review of the results of this protocol is contained in Dr. Gierhart's review and will not be summarized here. No unexpected safety issues were identified in the study, and the Sponsor has indicated that there are no new safety data to report which would warrant the submission of an additional safety report since the last report filed in Dr. Gierhart's study.

On March 9, 2004 Barr Research submitted an amendment to the pending NDA for Enjuvia™ 0.625 mg and 1.25 mg synthetic conjugated estrogens, B which contained the revised draft labeling. This label has been reviewed by the Division of Reproductive and Urologic Drug Products (DRUDP) and found to incorporate all of the recommendations contained in the February 2004 Guidance for Industry document “Labeling Guidance for Noncontraceptive Estrogen Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Prescribing Information for Health Care Providers and Patient Labeling”.

II Labeling

A. The negotiated label to be included in the Approval Letter to the Sponsor is attached.

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§ 552(b)(4) Draft Labeling

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/s/

Bruce Patsner
5/5/04 03:55:09 PM
MEDICAL OFFICER

Brenda Gierhart
5/5/04 04:02:21 PM
MEDICAL OFFICER

I concur with the Medical Officer's comments and recommendations.

MEDICAL TEAM LEADER MEMORANDUM

To: NDA 21-443

Through: Daniel Shames, MD
Director, HFD-580

From: Brenda S. Gierhart, MD
Medical Team Leader, HFD-580

Date: May 6, 2004

Re: Serial No. 000 AZ dated March 9, 2004
Enjuvia 0.625mg and 1.25 mg tablets
Duramed Pharmaceuticals, Inc.

Background:

- On March 22, 2002, Original NDA 21-443 was received for Enjuvia (synthetic conjugated estrogens) modified release tablets, [] 0.625, and 1.25 mg by Endeavor Pharmaceuticals.
- On May 6, 2002, a filing meeting was held and the NDA was accepted for filing with a user fee goal date of January 21, 2003.
- On May 16, 2002, a consult was sent to the Office of Postmarketing Drug Assessment requesting a tradename review. The trade name Enjuvia was found acceptable by Division of Medication Errors and Technical Support (DMETS) in two reviews dated September 24, 2002 and December 11, 2002.
- On May 16, 2002, a consult was sent to the Division of Drug Marketing, Advertising and Communications (DDMAC) requesting a label review. A formal response was received in a review dated November 12, 2002 and the comments were considered in the labeling negotiations.
- On May 16, 2002, a consult was sent to the Division of Surveillance, Research & Communication Support (DSRCS) requesting a label review. A review dated November 26, 2002 contained comments to the review division, which were considered in the labeling negotiations.
- On June 3, 2002, a request was sent to the Division of Scientific Investigations (DSI) listing 4 sites for inspection. On November 20, 2002 a Clinical Inspection Summary was sent by DSI stating that Dr. Ponder's site was NAI, Dr. Lenihan's site was VAI-RR due to being issued a Form 483 for several instances of failure to adhere to the protocol and to maintain adequate and accurate records, Dr. Eisenman's site was VAI due to being issued a Form 483 because two subjects took supplements with estrogenic properties, in violation of the protocol, and Dr. Gidwani's site was VAI due to certain essential elements of the consent form not being present, however a Form 483 was not issued. The overall conclusion was that the data submitted in support of NDA 21-443 by Drs. Eisenman, Lenihan, Gidwani, and Ponder appeared acceptable.
- On January 21, 2003, a major amendment containing study reports in support of the revised *in vitro/in vivo* correlation was submitted, which extended the user fee goal date to April 22, 2003.
- NDA 21-443 was then administratively split since the [] did not meet the division's standard for efficacy.
- On April 22, 2003, a not approvable letter was sent to [] for the Enjuvia [] mg tablets.
- On April 22, 2003, an approvable letter was sent to NDA 21-443 for the Enjuvia 0.625 and 1.25 mg tablets. The letter specified that before the application could be approved, draft labeling was to be submitted that incorporated the revisions to the package insert, carton, bottle, and blister labels sent to

the Sponsor on April 17, 2003 and the submission was to include a safety update. See Enjuvia Team Leader Review dated April 22, 2002.

- On May 8, 2003, a regulatory letter was sent to the Sponsor notifying them that the IVIVC submitted was not acceptable and the limitations were outlined in five bulleted comments.
- On May 21, 2003, the Division met with the Sponsor to discuss the “not approvable” issues associated with Enjuvia.
- On November 24, 2003, ownership of NDA 21-443 and [redacted] was transferred to Duramed Pharmaceuticals, a Barr subsidiary.
- In February 2004, a scientific article regarding the Phase 3 clinical trial supporting NDA 21-443 was published in *Obstetrics and Gynecology* (Utian WH, Lederman SA, Williams BM, Vega RY, Koltun WD and Leonard TW. Relief of Hot Flashes With New Plant-Derived 10-Component Synthetic Conjugated Estrogens. *Obstet Gynecol* 2004; 103; 245-53.)
- On February 11, 2004, a regulatory letter requesting incorporation of conjugated estrogens combined with medroxyprogesterone acetate data from the Women’s Health Initiative Memory Study (WHIMS), a substudy of the Women’s Health Initiative (WHI) into labeling was sent to the Sponsor.
- On March 10, 2004, a resubmission was received for NDA 21-443, which contained a complete, class 1 response to the April 22, 2003 action letter. The cover letter stated that no Safety Update was included in the submission since there were no new safety data, from either non-clinical or clinical studies on synthetic conjugated estrogens, B, to constitute a Safety Update. The regulatory letter dated March 4, 2004, which acknowledged the March 10, 2004, included a complete waiver for pediatric studies for NDA 21-443.

Resolution of all Consults and Discipline Issues related to current review cycle:

- On March 31, 2003, a consult to the Division of Medication Errors and Technical Support (DMETS) requesting a tradename review was sent. A review from DMETS dated February 4, 2004 stated that they had no objection to the proprietary name and that they had not reviewed the container labels and carton labeling as of the date of the review. A second review from DMETS dated April 26, 2004 contained comments on the bottle container labels and professional sample blister cards. These comments were taken into consideration during the labeling negotiations.
- On March 31, 2003, a consult to the Division of Drug Marketing, Advertising and Communications (DDMAC) requesting a tradename review was sent. DDMAC responded that their comments were included in the DMETS review and a separate response would not be sent from DDMAC.
- On March 31, 2003, a consult to the Division of Surveillance, Research & Communication Support (DSRCS) requesting a tradename review was sent. The reviewer from DSRCS, Jeanine Best, responded that their review finalized on November 26, 2002 would be the final review except for any Class labeling changes the Division needs to make. No formal response to the March 31, 2003 consult would be sent by DSRCS.
- Medical, Chemistry, Clinical Pharmacology and Biopharmaceutics, Pharmacology/Toxicology and Biometrics have no unresolved issues. A Biometrics memorandum was not written for the current review cycle. The Biometrics review for NDA 21-443 had been finalized on December 11, 2002. A Pharmacology/Toxicology memorandum was not written for the current review cycle. The Pharmacology/Toxicology review for NDA 21-443 had been finalized on January 22, 2003.

Summary of Labeling Negotiations:

On April 26, 2004, the Sponsor was faxed a draft 24 page Enjuvia Package Insert and Patient Information with all changes from the Sponsor proposed labeling submitted on March 9, 2004 highlighted, deletions marked with a single strike-through, and additions marked by a double underline.

On May 4, 2004, the Sponsor submitted a revised 24 page Enjuvia Package Insert and Patient Information by e-mail and stated that they had incorporated all of the Division's comments with the following exceptions:

- "Sodium" was added to the last structure (structure 10 in the Description section)
- [] in the Clinical Pharmacology section was deleted
- The Phase "Manufactured by" was deleted from the last page.

The proposed carton and blister labeling was also submitted by the Sponsor on May 4, 2004 attached to four separate e-mails.

Later on May 4, 2004, the Sponsor was contacted by teleconference. During the teleconference, the Sponsor clarified that [] had been deleted due to having insufficient time to create [] as requested by the Division and the following agreements were made regarding the Enjuvia Package Insert and Patient Information:

- 1) In the Boxed Warning on pg. 1 of 24, the extra space in the third sentence of the first paragraph between the words "than" and "synthetic" was deleted.
- 2) In the Boxed Warning on pg. 1 of 24, the box was enlarged to make visible the final two words of the box warning "individual woman."
- 3) Under Pharmacokinetics Absorption in the third sentence, the sentence beginning '[] and []' was changed to read "Table 1 and Table 2" since [] was deleted.
- 4) On pg 6 of 24 in Table 3, the superscript numeral "1" was deleted after the word "p-value" in Week 4 and in Week 12.
- 5) On pg 7 of 24 in Table 4, the superscript numeral "1" was deleted after the word "p-value" in Week 4 and in Week 12.
- 6) In the Women's Health Initiative Studies on pg. 7 of 24, the first sentence of the second paragraph [] was deleted since the CE substudy has been stopped and the results reported in JAMA.
- 7) In the subsection b. Venous thromboembolism (VTE) on pg. 10 of 24 in the second sentence, the phrase [] was deleted since the CE substudy has been stopped.
- 8) In the subsection 3. Dementia on pg. 12 of 24, the first two sentences of the second paragraph which reads [] were deleted since the CE substudy has been stopped.
- 9) In the subsection Geriatric Use on pg. 16 of 24, the first two sentences of the third paragraph which reads [] were deleted since the CE substudy has been stopped.
- 10) On pg. 24 of 24, it was clarified with the sponsor that the toll free number is still unknown and the XXX-XXX-XXXX will contain the toll free number prior to printing the label.
- 11) On pg. 24 of 24, it was communicated to the Sponsor that Chemistry has requested that they provide a qualifying statement immediately prior to DURAMED PHARMACEUTICALS such as "Distributed by:". The Sponsor agreed to add a qualifying statement and they sent a copy of the revised labeling that added the phrase "Distributed by:" in a e-mail on May 5, 2004.

Recommendation:

The Sponsor should be sent an approval letter for Enjuvia 0.625 and 1.25 mg tablets to include the negotiated labeling attached to this memorandum. N

cc: DFS NDA 21-443

HFD-580: D. Shames, B. Gierhart, B. Patsner, G. Lyght

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/s/

Brenda Gierhart
5/6/04 06:22:24 PM
MEDICAL OFFICER

Daniel A. Shames
5/7/04 11:32:08 AM
MEDICAL OFFICER