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APPLICATION NUMBER:
21-609

MEDICAL REVIEW

CLINICAL REVIEW

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Established Name Synthetic conjugated estrogens, B
(Proposed) Trade Name Enjuvia™
Therapeutic Class Estrogen (synthetic)
Applicant Barr Research, Inc.

Priority Designation Standard

Formulation Oral tablet
Dosing Regimen 0.3 mg daily
Indication Moderate to severe vasomotor
symptoms associated with the
menopause
Intended Population Post-menopausal women

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This Medical Officer recommends that Enjuvia™ 0.3 mg and 0.45 mg tablets be approved.

This Medical Officer finds that Enjuvia™ 0.3 mg and 0.45 mg tablets meet the Division of Reproductive and Urologic Drug Products' (DRUDP) safety and efficacy standard for approval of hormone therapy drug products for the treatment of moderate to severe vasomotor symptoms associated with the menopause. These recommendations are outlined in the January 2003 Guidance for Industry entitled "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation."

Enjuvia™ 0.3 mg has demonstrated adequate evidence of safety and efficacy in the reduction of the frequency and severity of moderate to severe hot flashes or vasomotor symptoms (VMS) at the 4 and 12 week endpoints in two clinical studies including one large, randomized, placebo-controlled clinical study of twelve weeks duration. In this Study (GA 326), women had a statistically significant reduction in both mean frequency and severity of moderate to severe VMS at the 4 and 12 week endpoints compared to those women who were treated with placebo.

Enjuvia™ 0.3 mg has also been shown to be safe for its intended use as recommended in the labeling by all means reasonably applicable to the assessment of safety. These include adverse events between groups in the clinical trials, review of laboratory data, and review of post-marketing reports from already approved hormone therapy products including AERS (Adverse Event Reporting System) updates. Sufficient data have been submitted and reviewed to provide adequate directions for use, including data that describe a safe and effective dose.

Approval of lower-dose Enjuvia™ 0.3 mg is also favored in light of the recently published data on the potential adverse cardiac and neoplastic side effects of combined estrogen-progestin therapy from the Women's Health Initiative (Writing Group for the Women's Health Initiative Investigators, Risk and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women. JAMA. 2002; 288: 321-333), as well as from estrogen therapy alone (Effects of Conjugated Equine Estrogen in Postmenopausal Women with Hysterectomy. JAMA 2004; 291: 1701-1712). DRUDP believes this data applies equally to synthetic as well as conjugated equine estrogens. FDA has great interest in promoting the use of the lowest effective dose of estrogen therapy for the shortest amount of time necessary to treat acute menopausal symptoms such as VMS.

Because Enjuvia™ 0.625 mg tablet has already been approved (NDA 21-443, March 28, 2003) and the sponsor has "bracketed" the 0.45 mg dose of Enjuvia™ between the 0.3 mg and 0.625 mg doses, Enjuvia™ 0.45 mg tablet should be approved as well.

The Division of Reproductive and Urologic Drug Products also recommend that the suggested labeling changes be adopted by the sponsor.

1.2 Recommendation on Post marketing Actions

This Medical Officer recommends no post marketing actions for the sponsor.

1.2.1 Risk Management Activity

No post marketing risk management activities are being recommended.

1.2.2 1.2.2 Required Phase 4 Commitments

No Phase 4 clinical study commitment requirement is being proposed.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests for the sponsor.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

A brief summary of the history of hormone therapy for acute menopausal symptoms (VMS, VVA) follows.

FDA has previously approved 5 drug products that contain conjugated estrogens: Premarin®, Prempro™, Premphase®, Cenestin®, and higher-dose (0.625 mg, 1.25 mg) Enjuvia™.

Premarin® (1.25 mg conjugated estrogens) was approved in 1942 for the relief of vasomotor symptoms (VMS). Premarin® contains a mixture of the estrogens estrone sulfate and sodium equilin sulfate with concomitant components. In 1972 Premarin® was found to be effective for several “DESI Indications” including moderate to severe vasomotor symptoms (MSVMS) associated with the menopause as well as eleven other indications including postmenopausal osteoporosis.

Wyeth-Ayerst received approval for NDA 20-303 on December 30, 1994 to market Prempro™ and Premphase®, two oral combination drug products consisting of conjugated estrogens (CE) and medroxyprogesterone acetate (MPA). Two dosage regimens were originally approved: Prempro™ 2.5 (0.625 mg CE/2.5 mg MPA) and Premphase® (0.625 mg CE/5mg MPA). At present Prempro™ and Premphase® (0.625mg/5mg) are all approved for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause in women with a uterus, treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA) associated with menopause, and prevention of postmenopausal osteoporosis.

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Additional estrogen hormone therapy products approved by DRUDP include other oral agents (Activella®, ClimaraPro®, Femhrt®, Prefest®, Estrace®), transdermals (Alora®, Climara®, Combipatch®, Esclim®, Estraderm®, Vivelle®, Vivelle Dot®), injections (Delestrogen®), vaginal tablets (Vagifem®), vaginal creams (Estrace®), and vaginal rings (Estring®, Femring®). Doses for these products vary.

Cenestin® (synthetic conjugated estrogens, A) was initially approved on March 27, 1999 for the treatment of moderate to severe VMS associated with the menopause. It is an oral estrogen product administered in tablet form that contains nine estrogenic substances (CE9) in combination: sodium estrone sulfate, sodium equilin sulfate and sodium 17 α -dihydroequilin sulfate, sodium 17 α -estradiol sulfate, 17 β -dihydroequilin sulfate, sodium 17 α -dihydroequilinen sulfate, 17 β -dihydroequilinen sulfate, sodium equilenin sulfate and sodium 17 β -estradiol sulfate. Three dosage strengths of Cenestin® (0.625 mg, 0.09 mg, and 1.25 mg) are approved for the treatment of MSVMS associated with the menopause. On June 17, 2002 FDA approved Cenestin® 0.3 mg for the treatment of vulvar and vaginal atrophy. On February 5, 2004 FDA approved the lower dose Cenestin® 0.45 mg tablet for treatment of MSVMS associated with the menopause.

Enjuvia™ (synthetic conjugated estrogens, B) is an oral estrogen product administered in tablet form that contains ten estrogenic substances (CE10) in combination, unlike Cenestin® which contains nine. At the time the original NDA 21-443 was submitted on March 21, 2002 Enjuvia™ was owned by Endeavor Pharmaceuticals; Endeavor was subsequently bought by Barr Pharmaceuticals. At the time of this writing Barr Pharmaceuticals owns both Enjuvia™ as well as Cenestin®.

NDA 21-443 S-000 originally sought marketing approval for treatment of MSVMS associated with menopause for four oral doses of Enjuvia™: 0.30 mg, 0.45 mg, 0.625 mg, and 1.25 mg. Approval for the two higher doses – 0.625 and 1.25 mg – was granted on April 22, 2003. However, approval for the two lower doses – 0.3 mg and 0.45 mg was denied in a Not Approvable letter sent to Endeavor, the original sponsor of the NDA, on April 22, 2003. Approval for the 0.3 mg dose was denied because it failed to meet all four efficacy endpoints, i.e. a statistically significant reduction in mean frequency and severity of moderate to severe hot flushes at both 4 and 12 weeks. Because the 0.45 mg dose was “bracketed” between the 0.3 mg and 0.625 mg doses and no independent efficacy data was submitted, approval for Enjuvia™ 0.45 mg dose was also denied.

Endeavor submitted a complete response to the non-approvable letter on August 29, 2003. This was accepted by DRUDP. On January 29, 2004 the August 29, 2003 submission was withdrawn by Barr Pharmaceuticals, the company which had recently acquired Endeavor.

Barr submitted the complete response which forms the basis for the NDA under consideration in this NDA review on June 29, 2004. DRUDP accepted this complete response, and set the 6-month PDUFA User Fee Goal date for this submission as December 30, 2004.

As no new pre-clinical data has been submitted by Barr Pharmaceuticals in support of this re-submitted NDA, all of the material exhaustively reviewed by Brenda Gierhart, M.D. in her March 28, 2003 original Primary Medical Officer Review is still relevant. Where referenced in this review it will be henceforth be referred to as "Dr. Gierhart's review".

1.3.2 Efficacy

One phase 3 Study (**GA 326**) was conducted and submitted to this NDA; this is the same clinical study which supported the original NDA application and which is considered the pivotal study for efficacy. The pharmacokinetic study (**ENDV-01-002**) is not pivotal.

The primary outcome variables for the efficacy study are reduction in frequency and reduction of severity of moderate to severe vasomotor symptoms (MSVMS) associated with the menopause. For estrogen products intended to treat moderate to severe vasomotor symptoms, DRUDP 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 mean frequency and mean severity of hot flushes in the treated groups compared with the control groups.

In the original submission from Endeavor a statistically significant reduction in both mean frequency and severity of moderate to severe vasomotor symptoms was not demonstrated for the subject group treated with Enjuvia™ 0.3 mg tablets to the compared to the group treated with placebo. However, the revised statistical analysis submitted by Barr in this complete response has demonstrated statistically significant reductions in mean frequency and severity of MSVSM for the same study using the same data. A detailed analysis of this data appears elsewhere in this review.

Because approval for Enjuvia™ 0.45 mg for the treatment of moderate to severe vasomotor symptoms was sought by bracketing the 0.45 mg dosage strength between the 0.3 mg tablet and the 0.625 mg tablet, independent efficacy data for the 0.45 mg dose is not required.

The **GA 326** study design was adequate with minimal opportunity for bias, and had adequately matched control groups. The study was sufficiently well-designed to allow the assessment of clinical benefit. The study was of adequate duration, employed appropriate entry criteria, tested an appropriate dose, and on re-analysis of study data was found to employ sound statistical analyses. The study did not exclude any major racial groups.

Enjuvia™ 0.3 mg and 0.45 mg tablets will provide a needed additional therapeutic option for treatment of MSVMS associated with menopause. Enjuvia™ is the second synthetic conjugated estrogen compound to be approved for this indication (Cenestin® was the first). Increased availability of lower-dose estrogen therapies for VSVMS is favored by both NIH and FDA.

1.3.3 Safety

All safety assessments were based on the safety population, i.e. all enrolled patients who received at least one dose of double-blind investigational product. All safety data was presented in the data listing. The duration of exposure to study drug was calculated in days from the first dose of investigational product to date of last dose of investigational product for each patient for each of the three four-week periods.

There were no deaths. Five patients experienced a total of 8 serious adverse events (SAE's) for all study subjects enrolled in GA 326. None of the serious adverse events were related to the study treatment according to the sponsor; Dr. Gierhart thought two of the 8 SAE's might potentially have been drug-related. 6% of study subjects had non-serious adverse events such as breast pain or minor gastrointestinal symptoms.

Data gathered was adequate to assess safety, and included adverse event monitoring during the trials and post-marketing data collected and continually updated in FDA's Adverse Event Reporting System (AERS). Based on this data, the safety profile of Enjuvia™ 0.3 mg and 0.45 mg is comparable to other currently approved estrogen therapy treatment available for MSVMS of menopause in the United States.

1.2.3 1.3.4 Dosing Regimen and Administration

The appropriate dosing regimen is one Enjuvia™ tablet taken daily. DRUDP recommends that patients being treated for VMS due to menopause be started at the lowest effective dose, which is the 0.3 mg dose.

In general, DRUDP suggests that menopausal women start hormone therapy for acute conditions such as VMS or VVA with the lowest effective dose, and that such dose be used for the shortest period of time necessary to provide adequate relief of acute menopausal symptoms. If a patient has already been started on one of the previously approved higher doses (e.g. 0.625 mg or 1.25 mg) of Enjuvia™ for treatment of VMS an effort should be made to titrate to the lowest dose for longer-term maintenance therapy.

1.2.4 1.3.5 Drug-Drug Interactions

No drug-drug interactions have been identified.

1.2.5 1.3.6 Special Populations

Enjuvia™ was investigated in postmenopausal women aged 25-65 years. No pharmacokinetic studies were conducted in other special populations.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The Barr synthetic conjugated estrogens,B product (CE10), Enjuvia™, contains 10 chemically synthesized estrogen sulfates as their respective sodium salts. The relative quantity of the 10 primary synthetic conjugated estrogens,B in CE10 were designed to match the specific ranges and limits defined by Conjugated Estrogens, USP based on their respective quantities in Premarin®. The modified release characteristics of CE10 were also designed to have comparable drug release profiles to Premarin®. In the Premarin® tablets, it is the _____ that results in the modified release product. The : _____

An approved synthetic conjugated estrogens,A product (CE9), Cenestin®, is also manufactured by Barr Pharmaceuticals. Cenestin® (Synthetic Conjugated Estrogens, A) is a 9-component estrogen product and differs from Enjuvia™ in that it lacks the component sodium Δ 8,9-dehydroestrone sulfate.

2.2 Currently Available Treatment for Indications

The currently available treatment for moderate to severe vasomotor symptoms (MSVMS) associated with menopause may be divided into two main categories: hormone therapy products and non-hormone therapy products.

Hormone therapy products include oral estrogens, transdermal estrogens, estrogen gels and creams, intravaginal estrogens, progestogens (pill, cream, or transdermal patch), and estrogen-progestogen combinations (pill, transdermal patch). FDA has currently approved products for treatment of MSVMS in all of these categories. A full discussion of all of the results of clinical trials for all of these hormone therapy products for treatment of MSVMS is beyond the scope of this NDA. A partial listing of the results of multiple trials comparing some of these hormone therapy drug products with placebo may be found in the recent review entitled "Vasomotor Symptoms" in the Supplement to the Journal Obstetrics and Gynecology (Obstet. Gynecol. 2004; 104:4 (S): 106S-117S. In addition, the recent article by H. Nelson, M.D. Ph.D. "Commonly Used Types of Postmenopausal Estrogen for Treatment of Hot Flashes. Scientific Review" (JAMA 2004; 291: 1610-1620) reviewed a total of 32 trials comparing the short-term efficacy and adverse effects of conjugated equine estrogens (CEE) and 17β -estradiol for treatment of VMS. This recent review demonstrated that both CEE and 17β -estradiol have consistent and comparable effects on treatment of VMS, and may have similar short-term adverse events.

Complimentary and alternative medicines which have been compared to placebo for treatment of MSVMS include wild yam extract, soy (tablet or extract), and black cohosh. Little clinical benefit has been demonstrated for these compounds thus far.

Other agents which have been used to treat MSVMS include Selective Serotonin Reuptake Inhibitors (SSRI's) such as Fluoxetine®, Paroxetine®, Setraline® and Venlafaxine®; anti-convulsive agents such as Gabapentin® and Aprepitant®; and Selective Estrogen Receptor Modulators (SERM's) such as Raloxifene®. In general, all of the SSRI compounds and Gabapentin® have shown some short-term success in the treatment of MSVMS though no long-term data or direct trials comparing them to hormone therapy currently exist. Vasomotor symptoms may actually worsen with the use of SERMs in postmenopausal women. None of the aforementioned agents are yet FDA-approved for treatment of hot flushes in postmenopausal women.

Overall, estrogens are currently considered the most effective treatment for post-menopausal vasomotor symptoms.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredients contained in Enjuvia™ are available in the United States.

Enjuvia™ 0.625 mg and 1.25 mg tablets are already FDA-approved and marketed in the United States as of 2003. There were no serious safety issues highlighted during the approval process for these higher doses of Enjuvia™, and the knowledge of the higher dose safety profile is directly applicable to this application for approval of the lower dose Enjuvia™ products. Safety risks for the lower doses (0.3 mg, 0.45 mg) tablets of Enjuvia™ are assumed to be either equal to or lower than those for the already approved higher dose (0.625 mg, 1.25) mg tablets already on the market in the US.

2.4 Important Issues With Pharmacologically Related Products

Indications for estrogenic hormone therapy products include treatment of acute menopausal conditions (VMS, VVA), chronic menopausal conditions (osteoporosis or prevention of osteoporosis), hypo-estrogenic conditions, and treatment of select malignancies in men and women.

Enjuvia™ (synthetic conjugated estrogens, B) 0.625 mg and 1.25 mg is approved for the treatment of MSVMS associated with menopause. Cenestin® (synthetic conjugated estrogens, A) 0.3 mg is approved for the treatment of vulvar-vaginal atrophy (VVA) associated with menopause, and Cenestin® 0.45mg, 0.625 mg, 0.9 mg, and 1.25 mg is approved for the treatment of VMS. These are the synthetic conjugated estrogen oral formulations currently approved for use in the US.

Premarin® (conjugated equine estrogens) 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, 1.25 mg and is approved for the treatment of VMS, VVA (0.3 mg to 1.25 mg/day), prevention of post-menopausal osteoporosis (0.625 mg/day); treatment of female hypoestrogenism due to hypogonadism, castration or primary ovarian failure (0.3mg or 0.625 mg/day); treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease (total dose of 30 mg/day for 3 months); and the treatment of advanced androgen-

dependent carcinoma of the prostate (for palliation only, 1.25 mg or 2x 1.25 mg three times daily).

In light of the recently published data on the potential adverse cardiac and neoplastic side effects of combined estrogen-progestin therapy from the Women's Health Initiative (Writing Group for the Women's Health Initiative Investigators, Risk and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women. JAMA. 2002; 288: 321-333) as well as potential risks from chronic use of unopposed estrogen therapy (Effects of Conjugated Equine Estrogen in Postmenopausal Women with Hysterectomy. The Women's Health Initiative Randomized Controlled Trial. JAMA. 2004; 291: 1701-1712), FDA clearly has a great interest in promoting the use of the lowest effective dose of hormone therapy for the shortest amount of time necessary for the treatment of non-chronic menopausal conditions such as VMS associated with menopause.

Although there is no conclusive data which definitively proves that lower doses of estrogen such as 0.3 mg or 0.45 mg are actually safer than higher doses such as 0.625 or 1.25 mg, there are theoretical and clinical reasons why the cardiac, thrombo-embolic, and other risks might be lower. For these reasons the lower doses should certainly be at least as safe as the higher doses which have already been approved by FDA. This renewed emphasis on "lowest effective dose for the shortest duration necessary" for treatment of acute conditions during menopause favors approval of Enjuvia™ 0.3 mg, particularly since all recent epidemiological data since the July 2002 WHI report indicates that many patients are either discontinuing hormone therapy or are tapering to lower doses (National Use of Postmenopausal Hormone Therapy. Annual Trends and Response to Recent Evidence. JAMA. 2004; 291: 47-53).

2.5 Presubmission Regulatory Activity

An abbreviated summary of the presubmission regulatory activity prior to that described in this is contained in Shelley Slaughter M.D.'s Team Leader Review of Enjuvia™ NDA 21-443/21-609 dated April 22, 2003.

An extensive summary of the important milestones in the development of Enjuvia and the significant regulatory interactions and decisions appears in section 3.3.1 of Dr. Gierhart's NDA review which recommended approval of Enjuvia™ 0.625 mg and 1.25 mg tablets. It is not necessary to repeat all of this information in this NDA review.

In addition, a review of the pre-submission regulatory activity also appears in Section 1.3.1 ("Brief Overview of Clinical Program") of this NDA Medical Officer Review.

2.6 Other Relevant Background Information

The most recent regulatory history of Enjuvia™ 0.3 mg and 0.45 mg tablets may be summarized.

Endeavor, the original sponsor of the NDA, was issued a not approvable letter 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 on April 22, 2003. A complete response to the not approvable letter was submitted to DRUDP on August 29, 2003, and was accepted by the Division. In the interim, Endeavor was acquired by Barr Research. On January 28, 2004, the August 29th submission was formally withdrawn by Barr. On June 29, 2004 Barr submitted a new response to the Division's April 22, 2003 not approval letter. This June 29, 2004 response was accepted by the Division as a complete response on July 29, 2004. This complete response submitted by Barr included a major statistical re-analysis of the original data submitted in support of the original application. This statistical re-analysis is central to the current NDA approval, as the only reason why Enjuvia™ 0.3 mg tablets was denied the approval granted to Enjuvia™ 0.625 and 1.25 mg tablets was because of a failure of the lowest dose to achieve a statistically significant reduction, when compared to placebo, in mean frequency and severity of moderate to severe vasomotor symptoms associated with the menopause within 4 weeks of start of therapy.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Enjuvia™ (synthetic conjugated estrogens, B) tablets contain a blend of ten (10) chemically synthesized estrogen sulfates as their respective sodium salts. The estrogenic substances are:

1. Sodium estrone sulfate
2. Sodium equilin sulfate
3. Sodium 17 α -dihydroequilin sulfate
4. Sodium 17 α -estradiol sulfate
5. Sodium 17 β -dihydroequilin sulfate
6. Sodium 17 α -dihydroequilenin sulfate
7. Sodium 17 β -dihydroequilenin sulfate
8. Sodium equilenin sulfate
9. Sodium 17 β -estradiol sulfate
10. Sodium Δ 8,9-dehydroestrone sulfate

Cenestin® (synthetic conjugated estrogens, A) is a 9-component estrogen product which differs from Enjuvia™ in that it lacks the sodium Δ 8, 9-dehydroestrone sulfate.

3.2 Animal Pharmacology/Toxicology

No clinical pharmacology or toxicology studies were conducted. A summary of the relevant literature was submitted to support NDA 21-443 in the corresponding Nonclinical Pharmacology and Toxicology section.

The Pharmacology/Toxicology review finalized on January 22, 2003 concluded that additional toxicology studies were not needed or appropriate to support the safety of Enjuvia™ because:

- Conjugated estrogens and estrogens in general have been the subject of substantial toxicological evaluations.

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- Any difference in toxicity between approved estrogen products and Enjuvia™ would be expected to be small and subtle. No current animal toxicology studies have the power to detect such small differences, if they exist at all, and the applicability of any small measured differences from such preclinical testing would be questionable.

Please see the Pharmacology/Toxicology review for NDA 21-443.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary sources of data used in this review are the clinical trials conducted by the original sponsor Endeavor, now property of the current sponsor Barr Pharmaceuticals. These clinical trials include the primary clinical trial GA 326 and ENDV-01-002, the primary pharmacokinetic trial. Additional safety support relies on FDA's Adverse Event Reporting System (AERS) Data Mart. As of 12/06/04 no new serious reports have been entered into the system for NDA 21443 (Enjuvia™). Literature searches were performed, including the Pub Med and Micromedix databases, to provide further information on safety. No new safety concerns, nor serious adverse events, have arisen since the original submission of this NDA.

4.2 Tables of Clinical Studies

Study Number	Study Type	Study Title	Number of Subjects	Efficacy Evaluation	Safety Evaluation
ENDV-01-002	Pharmacokinetic	"A Single-Dose, Fasting, Pharmacokinetic Study to Determine the Bioavailability of Synthetic Conjugated Estrogens (CE10 0.625 mg Modified-Release Tablets) in Postmenopausal Women"	21	21	21
GA 326	Clinical Phase 3	"A Randomized, Double-Blind, Dose-Ranging,	281	276	281

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		Parallel-Group Study to Compare the Safety and Efficacy of Synthetic 10-Component Conjugated Estrogens (CE10) (0.3, 0.625, and 1.25 mg modified release) with Placebo in Postmenopausal Women Suffering from Moderate to Severe Vasomotor Symptoms”			
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ENDV-01-002 was a single center, open-label, single-dose pharmacokinetic study in 21 healthy fasting postmenopausal women conducted at one site in Fargo, North Dakota. The objective of the study was to determine the plasma profile of a ten-component synthetic conjugated estrogens (CE10) oral tablet product following administration to post-menopausal women.

Study **GA 326** was a Phase 3, multi-center, 12-week investigational drug treatment duration, randomized, double-blind, dose-ranging, parallel-group, placebo-controlled efficacy and safety study comparing the efficacy, safety, and tolerability of 3 different doses of CE10 (0.3, 0.625, and 1.25 mg modified release) versus placebo in the treatment of moderate to severe vasomotor symptoms in 281 postmenopausal women aged 25 to 65 years.

For Study **GA 326**, a total of 281 patients were randomized to one of four treatment groups from twenty-two US sites that enrolled one or more patients. Five (5) patients in the All Enrolled population were excluded from the ITT population. The patients excluded from the ITT population were four patients who were lost to follow-up after the randomization visit and one patient who was discontinued after one dose of study medication due to not meeting an exclusion criterion. Fifty-six (56) patients in the All Enrolled population were excluded from the PP population. The patients excluded from the PP population were 53 patients who did not complete 12 weeks of treatment and 3 additional patients who had protocol violations related to an inclusion or exclusion criterion.

Definitions for the different study populations were as follows:

- All Enrolled population: patients who met the inclusion/exclusion criteria and had data in the demographics dataset. The All Enrolled population is in some tables listed as the All Randomized population.
- Safety population: All enrolled patients who received at least one dose of double blind investigational product.
- ITT population: all randomized patients who took at least one dose of study drug and who had at least one complete day of pre-treatment and post-treatment primary efficacy assessments (i.e. one complete day of diary data recorded).
- PP population: the protocol defined this population as those patients who fulfilled all inclusion criteria, who did not fulfill any exclusion criteria, who took the investigational product according to the protocol, who had valid week 4 and week 12 assessments, and who had no significant protocol violations, as determined by the Principal Investigator and agreed to by the Sponsor prior to unblinding the study treatment codes. The Final Study Report added an additional definition that the PP population included those patients who achieved a study drug compliance rate $\geq 80\%$.

4.3 Review Strategy

Sources used for writing this review included

- The two studies listed above – **GA 326** and **ENDV-01-002**
- The original Medical Officer Review by Dr. Gierhart and Team Leader Review by Dr. Slaughter for NDA 21-443
- The Medical Officer NDA Review for approval of Cenestin® (synthetic conjugated estrogens, A) by Bruce Patsner, M.D.
- Review of all Memoranda of Statistical Review prepared by Moh-Jee Ng, M.S. and Mike Welch Ph.D.
- _____
- Minutes of all regulatory meetings and telephone conferences, and all relevant correspondence, with Barr Pharmaceuticals that were contained in DRUDP files
- Conjugated estrogens Healthcare Provider and Patient labeling
- Synthetic conjugated estrogens Healthcare Provider and Patient labeling

The primary review issue for this NDA is whether the reanalysis of the efficacy data from Study **GA 326** by Barr Pharmaceuticals now demonstrates a statistically significant decrease in mean frequency and severity of MSVMS associated with menopause compared to placebo at both the 4 and 12 week endpoints.

4.4 Data Quality and Integrity

An overview of methods used to evaluate data quality and integrity for Study **GA 326** follows.

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DSI audits. DRUDP requested that the Division of Scientific Investigation (DSI) audit four study centers that participated in Study **GA 326**. When the sites were evaluated by DSI for the number of randomized subjects, it was noted that ten of the total twenty-two sites had the largest numbers of randomized subjects (between 16-21 subjects per site). The four sites selected for inspection each randomized between 16-21 subjects.

A summary of the results of all DSI audits is contained in Dr. Gierhart's March 28, 2003 Medical Officer NDA Review of NDA 21-443. Findings at the four sites - #'s 103, 111, 112, and 120 – varied from no discrepancies found (103, 120) to minor protocol violations (111) to failure to adhere to protocol or maintain adequate and accurate records (112) for which Voluntary Action Indicated (VAI).

Central laboratory. For Study **GA 326**, a central laboratory _____ performed standardized laboratory procedures.

For Study **ENDV-01-002**, pharmacokinetic blood samples were frozen and upon completion of _____

No significant discrepancies were noted.

Site monitoring. For Study **GA 326**, clinical monitoring was performed before, during, and after the trial by _____. The monitor checked the accuracy and completeness of the _____ source documents, and other trial-related records against each other.

No significant discrepancies were noted.

4.5 Compliance with Good Clinical Practices

The content of the informed consent form was adequate and the sponsor obtained consent before enrollment in Study **GA 326** as specified in the protocol. In terms of protocol violations, the DSI site visits were able to document a small number of protocol violations, of which two involved the use of prohibited medications (dietary supplements with estrogenic properties) at site #111. At site #103 it was noted that the consent form used in the study did not conform to the requirements of 21 C.F.R. 50.25(a). A form 483 was not issued, and no response was required. Reviews of results from the various sites did not produce questions of serious unusual results at any particular center. There was no apparent need for the review team or others (e.g. consultants, special government employees) to audit the case report forms (CFR's) or clinical source data.

4.6 Financial Disclosures

The sponsor submitted a total of 7 pages of financial disclosure information in NDA 21-443 volume 1 for Investigators who participated in Study **GA 236** and Study **ENDV-01-002**. Review of this information by Dr. Gierhart, and re-review of this information by this Medical Officer allows the following conclusions:

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- the information was complete
- the appropriate document was received
- the information complied with 21 CFR 54
- no discloseable information was reported, except regarding site #103 in GA 326
- no conflicts of interest were noted, except regarding site #103 in GA 326
- there was no disclosure of financial interests that could bias the outcome of trials, except regarding site #103 in GA 326.

Because of financial disclosure information by one sub-investigator at site #103, the twenty patients from this site who were randomized to Study GA 326 (7.1% of the total of 281 patients who were randomized) were dropped from efficacy calculations performed by Biometrics at DRUDP. Results of the re-calculation of the data for Study GA 326 once these patients were dropped had the following effects:

- it did not eliminate the statistically significant decrease in mean change in frequency and severity of MSVMS of Enjuvia™ 0.625 mg and 1.25 mg tablets compared to baseline
- it did result in Enjuvia™ 0.3 mg now demonstrating a statistically significant decrease in mean frequency of hot flushes from baseline compared to placebo at the 4 week endpoint. No significant improvement in mean change in severity of MSVMS was demonstrated though the other endpoints were met.

Because no fundamental change in the efficacy conclusions of the original statistical analysis resulted from the elimination of study subjects from site #103, no bias due to financial disclosure concerns was found.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

No pharmacokinetic data was generated by the conduct of Study GA 326.

The pharmacokinetic data generated by the conduct of Study ENDV-01-002 was reviewed in detail in Appendix B of Dr. Gierhart's review. Study ENDV-01-002 entitled "A Single-Dose, Fasting Pharmacokinetic Study to Determine the Bioavailability of Synthetic Conjugated Estrogens (CE10 0.625 mg Modified-Release Tablets) in Postmenopausal Women" ran from July 9, 2001 through July 13, 2001. This was a Phase 2, single-center, open-label, single-dose pharmacokinetic study in 21 healthy, fasting postmenopausal women conducted at one site in Fargo, North Dakota with Alan K. Copa as the principal investigator. Mean pharmacokinetic parameters for unconjugated and conjugated estrogens in healthy postmenopausal women under fasting conditions were calculated.

In Study ENDV-01-002, no new or unexpected safety issues were identified. Please see the original Clinical Pharmacology and Biopharmaceutics review for NDA 21-443 for their

assessment of efficacy. The pharmacology reviewer concluded that no toxicity relevant to the proposed clinical use was observed, and there were no clinical safety issues relevant to clinical use.

The supportive pharmacokinetic data generated with the 9 component conjugated estrogen (CE9) studies consisted of four single dose studies: GEN-US-04, GEN-US-05, GEN-US-06, and GEN-US-07. Studies GEN-US-05 and GEN-US-07 were three-way, open-label, randomized crossover bioequivalence studies comparing 0.625 mg and 1.25 mg CE9 fed and fasted to Premarin fed. Studies GEN-US-04 and GEN-US-06 were two-treatment, open-label, randomized crossover bioequivalence studies comparing 0.625 mg and 1.25 mg CE9 and Premarin.

5.2 Pharmacodynamics

No pharmacodynamic data were generated by the conduct of the Study GA 326 to study the mechanism of action of Enjuvia™

5.3 Exposure-Response Relationships

Based on NDA 21-443 for Enjuvia™ 0.625 mg and 1.25 mg tablets, no new information has been submitted for the exposure-response relationships for the current proposed lower (0.3 mg and 0.45 mg) doses of Enjuvia™.

In general, the higher the initial starting doses of hormone therapy for MSVMS, the more rapid and dramatic the relief of MSVMS in post-menopausal women. This dose-response relationship is more pronounced for acute menopausal symptoms such as VMS and VVA, and holds especially true for women who have recently become symptomatic, i.e. having recently become post-menopausal. Differences in rapidity of onset of relief of VMS among different doses of estrogens notwithstanding, a statistically significant mean reduction in both frequency and severity of MSVMS associated with menopause is achieved within 4 weeks of initiation of therapy of oral Enjuvia™. (See next Section: Integrated Review of Efficacy).

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

6.1.1 Methods

Study GA 326 was the primary clinical trial originally conducted by Endeavor Pharmaceuticals to support the indication of treatment of moderate to severe vasomotor symptoms associated with the menopause.

Study ENDV-01-002 was the supportive, open-label pharmacokinetic (PK) bioavailability study.

6.1.2 General Discussion of Endpoints

The primary efficacy parameters as stated in Protocol GA-326 were the following:

- Reduction in frequency of moderate to severe hot flashes from baseline to week 4 and to week 12 in treated groups compared to the control group.
- Reduction in severity of vasomotor symptoms from baseline to week 4 and to week 12 in the treated groups compared with the control group.

Both of these efficacy parameters are consistent with the clinical endpoints DRUDP recommends for hormone therapy for treatment of VMS associated with menopause in its 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.”

Additional secondary efficacy parameters as stated in Protocol GA-326 included:

- Reduction in frequency of moderate to severe hot flashes from baseline to week 8 in the treated groups as compared to the control group.
- Reduction in severity of vasomotor symptoms from baseline to week 8 in the treated groups compared to the control group.
- Change in the Kupperman Index total score from baseline to 4, 8, and 12 weeks of

treatment.

- Relief of urogenital symptoms (i.e. vaginal itching/dryness, urinary discomfort, urinary frequency, and dyspareunia) as assessed by the change from baseline to weeks 4, 8, and 12 of treatment.
- Patient and Physician Global Assessment of Effectiveness of the Study Drug. The overall effectiveness of the study drug will be assessed after 12 weeks of treatment by the patient and the investigator, using the categories “excellent”, “good”, “fair”, and “poor”.

No drug concentration measurements were made during Study **GA 326**.

In Study **ENDV-01-002**, primary C_{max}, T_{max}, t_{1/2}, AUC_{0-t}, AUC_∞, and k_{elim}, pharmacokinetic parameters were determined for free and total estrone, equilin, and Δ 8,9-dehydroestrone (DHE) following a single dose of Enjuvia® 0.625 mg x 2 tablets.

6.1.3 Study Design

Study **GA 326** was a Phase 3, multicenter, 12-week investigational drug treatment duration, randomized, double-blind, dose-ranging, parallel-group, placebo-controlled efficacy and safety study of Enjuvia™ 0.3 mg, 0.625 mg and 1.25 mg tablets in 281 postmenopausal women aged 26 to 65 years for the treatment of moderate to severe vasomotor symptoms.

Study **ENDV-01-002** was an open-label, pharmacokinetic (PK) bioavailability study evaluating standard PK parameters for free and total estrone, equilin, and Δ8, 9-dehydroestrone (DHE) following a single dose of Enjuvia™ 0.625 mg x 2 tablets in postmenopausal women.

6.1.4 Efficacy Findings

The current sponsor, Barr Pharmaceuticals, provided a new statistical analysis of efficacy in response to the not approvable letter dated April 22, 2003. These new results, based on a non-parametric analysis, demonstrate that subjects who received Enjuvia™ 0.3 mg tablets demonstrated a statistically significant reduction in both mean frequency and severity of moderate to severe vasomotor symptoms (MSVMS) associated with menopause compared to placebo at both the 4 and 12 week endpoints.

Although the original statistical analysis by Endeavor and the new statistical analysis by Barr both concern the same clinical study – **GA 326** – the findings do differ. The reason for this becomes apparent when the statistical methodology used in both cases is evaluated..

In the original NDA submission, the sponsor's (Endeavor's) efficacy analysis using DRUDP's recommended clinical endpoints was based on analysis of covariance (ANCOVA) with baseline, treatment, center, and treatment-by-center interaction. Although the protocol indicated that a non-parametric analysis (such as rank-based observations or a stratified Wilcoxon test) would be applied if the ANCOVA model did not fit the data well, this was not done. In other words, even

though Endeavor's data in **GA 326** showed significant departures from the normality assumption, Endeavor did not include a non-parametric analysis.

As a result of this omission, the data for Enjuvia™ 0.3 mg failed to achieve a statistically significant reduction in both frequency and severity of MSVMS at the 4 week endpoint; only the higher (0.625 mg and 1.25 mg) doses did. Because Enjuvia™ 0.45 mg was bracketed between the 0.3 mg dose and the 0.625 mg dose, the 0.45 mg dose data automatically failed to achieve statistical significance and it too was not approved.

The original frequency and severity data, submitted by Endeavor, is in Tables One and Two which are listed below.

In the complete response package dated June 29, 2004, the new sponsor (Barr Pharmaceuticals) re-analyzed all of the primary efficacy results using a rank-based procedure. This method essentially applies an ANCOVA procedure to the ranked observations. Barr had to use a non-parametric analysis because the variables were not normally distributed.

The results of this re-analysis demonstrated that Enjuvia™ produced a statistically significant reduction in frequency and severity of MSVMS compared to placebo at 4 and 12 weeks. This re-analysis of the original data is contained in Tables Three and Four shown below, all based on the ITT population. (This data also appears in Table Five in the sponsor's complete response package)

Tables One, Two, Three, and Four illustrate the original and revised efficacy analyses, respectively, for Study **GA 326**:

- Table One lists the original efficacy findings for reduction in mean frequency of MSVMS at the 4 and 12 week endpoints.
- Table Two lists the original efficacy finds for the reduction in mean severity of MSVMS at the 4 and 12 week endpoints.
- Table Three lists the new efficacy findings for the reduction in mean frequency of MSVMS at the 4 and 12 week endpoints
- Table Four lists the new efficacy findings for the reduction in mean severity of MSVMS at the 4 and 12 week endpoints.

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**Table One. Reduction in Frequency of Moderate to Severe Hot Flushes
 – Original Submission**

	CE10 0.3 mg N=66	CE10 0.625 mg N=71	CE10 1.25 mg N=69	Placebo N=70
Baseline				
Mean (SD) Number per week	104.3 (57.7)	97.3 (82.1)	86.8 (42.1)	96.4 (58.2)
Week 4				
Mean (SD) Number per week	47.0 (52.9)	23.3 (26.9)	24.6 (47)	57.8 (47.5)
LSMean (SE) Change from Baseline	-49.8 (5.2)	-72.8 (5.0)	-68.3 (5.1)	-37.2 (5.0)
Pairwise Comparison (p-value) ¹	0.0821	<0.0001	<0.0001	-----
Week 8				
Mean (SD) Number per week	34.8 (50.8)	13.0 (17.8)	13.8 (27.3)	49.5 (47.9)
LSMean (SE) Change from Baseline	-61.8 (4.6)	-83.0 (4.4)	-80.2 (4.5)	-45.9 (4.5)
Pairwise Comparison (p-value) ¹	0.0136	<0.0001	<0.0001	-----
Week 12				
Mean (SD) Number per week	30.7 (47.7)	12.2 (18.7)	12.4 (26.6)	47.5 (49.8)
LSMean (SE) Change from Baseline	-66.3 (4.6)	-84.6 (4.4)	-82.6 (4.5)	-48.3 (4.5)
Pairwise Comparison (p-value) ¹	0.0051	<0.0001	<0.0001	-----

Source:

SD = Standard Deviation; SE = Standard Error; LSMea = Least Squares Mean; Mean = Arithmetic Mean

¹p-value for pairwise comparison to placebo is significant when p<0.05

**Table Two. Reduction in Severity of Moderate to Severe Hot Flashes
 –Original Submission**

	CE10 0.3 mg N=66	CE10 0.625 mg N=71	CE10 1.25 mg N=69	Placebo N=70
Baseline				
Mean (SD)	2.3 (0.4)	2.4 (0.3)	2.4 (0.4)	2.4 (0.4)
Week 4				
Mean (SD)	1.9 (0.6)	1.7 (0.9)	1.4 (1.0)	2.1 (0.8)
LSMean Change from Baseline (SE)	-0.5 (0.1)	-0.7 (0.1)	-1.0 (0.1)	-0.3 (0.1)
Pairwise Comparison (p-value) ¹	0.3105	0.0092	<0.0001	-----
Week 8				
Mean (SD)	1.6 (0.9)	1.4 (1.0)	1.0 (1.0)	1.9 (0.9)
LSMean Change from Baseline (SE)	-0.8 (0.1)	-1.0 (0.1)	-1.4 (0.1)	-0.5 (0.1)
Pairwise Comparison (p-value) ¹	0.0606	0.0007	<0.0001	-----
Week 12				
Mean (SD)	1.5 (1.0)	1.1 (1.1)	1.0 (1.0)	1.9 (0.9)
LSMean Change from Baseline (SE)	-0.9 (0.1)	-1.3 (0.1)	-1.4 (0.1)	-0.5 (0.1)
Pairwise Comparison (p-value) ¹	0.0181	0.0181	<0.0001	-----

Source:

SD – Standard Deviation; SE = Standard Error; LSMean = Least Squares Mean; Mean = Arithmetic Mean

¹p-value for pairwise comparison to placebo is significant when p<0.05

In Study GA 326 for the Intent-to-Treat population, statistically significant changes in the frequency and severity of MSVMS from baseline to Weeks 4, 8, and 12 when compared with placebo were documented for the CE10 0.625 and 1.25 mg treatment groups.

The Enjuvia™ 0.3 mg treatment group:

- (1) failed to demonstrate a statistically significant change in the mean frequency of MSVMS from baseline to Week 4 when compared to placebo; and
- (2) failed to demonstrate a statistically significant change in the mean severity of MSVMS from baseline to Week 4 and to Week 8 when compared to placebo.

Statistically significant reductions were not reached for frequency until Week 8, and not reached for severity until Week 12 in the original data analysis.

Barr's re-analysis of the data notwithstanding, DRUDP's statistical reviewers do not recommend the use of ANCOVA applied directly to the ranked-based observations. The non-parametric analysis methodology favored by DRUDP is the stratified Wilcoxon test, and this methodology was applied to Barr's data in GA 326. In this approach the tests for statistical significance are based on the Wilcoxon test though the descriptive statistics (e.g. least squares mean change, standard errors, etc.) are based on the parametric ANCOVA. (See Statistics Review).

Using the DRUDP preferred analysis instead of the sponsor's, the significance levels and descriptive statistics were still consistent with the sponsor's re-analysis. However analyzed by either Barr or DRUDP, these results show that the changes from baseline in the frequency and severity endpoints at weeks 4 and 12 are statistically significant between the Enjuvia™ and the placebo groups.

The re-analysis data performed by DRUDP for reduction in mean frequency and severity of MSVMS at the 4 and 12 weeks endpoints is shown in Tables Three and Four.

Table 3. Mean Change from Baseline in Frequency of MSVS per week in the ITT^a using LOCF^b Analysis – New Analysis

Week	Placebo N=70	Enjuvia 0.3 mg N=66
Baseline [1]		
Mean (SD)	96.4 (58.2)	104.3 (57.7)
Week 4*		
Mean (SD)	57.8 (47.5)	47.0 (52.9)
Mean change from baseline (SE)	- 39.2 (5.8)	- 52.9 (6.0)
P-values [2]		0.0164
Week 8		
Mean (SD)	49.8 (47.9)	34.8 (50.8)
Mean change from baseline (SE)	- 47.9 (5.8)	- 64.8 (6.1)
Week 12*		
Mean (SD)	47.5 (49.8)	30.7 (47.7)
Mean change from baseline (SE)	- 50.5 (5.7)	- 69.7 (6.0)
P-values [2]		0.0075

Sources: SAS dataset

^aITT=Intent-to-Treat, ^bLOCF=Last Observation Carried Forward.

Mean change is ANCOVA adjusted mean change. LSMean=Least Square Mean, SD=Standard Deviation, SE= Standard Error, CI=Confidence Interval.

* : Primary endpoint

[1]: The number of MSVS at baseline was the weekly average number of MSVS using the last 14 days of diary data that were recorded prior to randomization
 [2]: P-values based on Wilcoxon rank sum test (Van Elteren test)

Table 4. Mean Change from Baseline in Severity [1] of MSVS per week in the ITT^a using LOCF^b Analysis – New Analysis

Week	Placebo N=70	Enjuvia 0.3 mg N=66
Baseline [2]		
Mean (SD)	2.5 (0.3)	2.5 (0.3)
Week 4*		
Mean (SD)	2.2 (0.8)	2.1 (0.8)
Mean change from baseline (SE)	-0.3 (0.1)	-0.5 (0.1)
P-values [3]		0.0218
Week 8		
Mean (SD)	2.1 (0.9)	1.7 (1.1)
Mean change from baseline (SE)	-0.5 (0.1)	-0.8 (0.1)
Week 12*		
Mean (SD)	1.9 (1.1)	1.5 (1.2)
Mean change from baseline (SE)	-0.6 (0.1)	-1.0 (0.1)
P-values [3]		0.0239

Sources: SAS dataset

^aITT=Intent-to-Treat, ^bLOCF=Last Observation Carried Forward.

Mean change is ANCOVA adjusted mean change. SD=Standard Deviation, SE=Standard Error

* : Primary endpoint, statistically significance at 0.05 level is marked gray

[1] Severity = (2*nr_mod + 3*nr_sev) / (nr_mod + nr_sev)

where nr_mod and nr_sev were the numbers of moderate and severe hot flushes

[2]: The number of MSVS at baseline was the weekly average number of MSVS using the last 14 days of diary data that were recorded prior to randomization

[3]: P-values based on Wilcoxon rank sum test (Van Elteren test)

6.1.5 Efficacy Conclusions

Barr Pharmaceuticals has adequately demonstrated that use of Enjuvia™ 0.3 mg tablets results in a statistically significant decrease in the mean frequency and severity of moderate to severe hot flushes due to menopause when compared to placebo after 4 and 12 weeks of continuous use.

Because the sponsor achieved statistical significance for the primary efficacy endpoints for Study GA 326 for the 0.3 mg dose, the 0.3 mg and dose of Enjuvia™ tablets should be approved. The 0.45 mg dose of Enjuvia™ should also be approved because it is bracketed between the 0.3 mg and 0.625 mg doses.

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7 INTEGRATED REVIEW OF SAFETY

No unexpected safety issues were identified during this review.

A comprehensive review of the safety findings of Study **GA 326** is contained in Dr. Gierhart's NDA review. Important findings will be summarized here.

7.1 Methods and Findings

7.1.1 Deaths

No deaths occurred during any of the Studies (**GA 326** or **ENDV-01-002**) conducted with Enjuvia™. There are no reported deaths in the adverse event literature for Enjuvia™.

7.1.2 Other Serious Adverse Events

There were no serious adverse events for Study **ENDV-01-002**.

All reported serious adverse events were considered unrelated to treatment for study **GA 326** according to the Sponsor. Dr. Gierhart believed that two of the serious adverse events – one episode of cholecystitis and one cerebrovascular accident – might have been drug-related. Given the fact that there was a total of only 5 SAE's for Study **GA326**, no definitive analysis of the relationship between Enjuvia™ dose and Adverse Events may be done.

A table summarizing SAE's for Study **GA 326** is below.

GA326 Treatment Emergent SAE's by Treatment Group (All Enrolled Patients)

Site#/ Patient #	Age (yrs)	Treatment Group	Onset Date/ Time to SAE onset (days)	Serious Adverse Event	Relationship to Treatment*/Action Taken/Outcome
108/0173	40	CE10 0.3 mg	April 9, 2001 (53)	Accidental injury; Fracture of left ankle	Unrelated/ Discontinuation/ Resolved
101/0125	43	CE10 0.3 mg	March 23, 2001 (39)	Cholecystitis	Unrelated/ Discontinuation/ Resolved
105/0082	61	CE10 0.625 mg	January 12, 2001 (32)	Cerebrovascular accident	Unrelated?/None ¹ Resolved
108/0238	44	CE10 1.25 mg	May 26-28, 2001 (57-59)	Acute exacerbation of COPD, ARG	Unrelated/ Discontinuation/ Resolved
103/0250	40	Placebo	June 5, 2001 (16)	Dehydration for 4 days	Unrelated/ Discontinuation/ Resolved ²

*Relationship to study drug based on assessment by investigator

¹ Patient had discontinued study drug three days prior to occurrence of SAE and lost to follow-up

² Patient had three separate episodes of dehydration that were listed as separate SAE's

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

A summary of **GA 326** patients who prematurely terminated due to adverse events for all enrolled patients appears in Dr. Gierhart's review in Table 24 on p. 53.

7.1.3.2 Adverse events associated with dropouts

No patients terminated prematurely from Study **ENDV-01-002** because of safety reasons.

For Study **GA 326** a total of 18 patients (6.4%) discontinued prematurely during the 12-week treatment period due to an adverse event. Four (4) of these 18 patients discontinued prematurely from the study as a result of a Serious Adverse Event (SAE).

The number of patients who discontinued due to Adverse Events (AE's) did not clearly increase with increasing Enjuvia™ dose.

7.1.3.3 Other significant adverse events

Non-serious adverse events that occurred in the clinical trials that did not necessarily lead to discontinuation in the trial are described in this section.

7.1.4 Other Search Strategies

None.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

During all of the clinical trials, the Investigator questioned subjects at every visit about adverse events using an open question, and was instructed not to influence the subjects' answers. Adverse event information was collected at the same time the patient diaries were reviewed.

All adverse events, either reported verbally by the patient or observed by the Investigator, were transcribed onto the Case Report Form (CRF). On that form, events were described and classified. When an adverse event persisted at the end of the study, the Investigator ensured that

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there was follow-up of the subject until the Investigator agreed the event was satisfactorily resolved. One study subject with a serious adverse event in the treatment group was lost to longer-term follow-up.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The groups closely related Investigator or subject reported terms used the MedDRA dictionary of preferred terms. DRUDP is not concerned that use of these preferred terms resulted in a missed “signal” for Enjuvia™.

7.1.5.3 Incidence of common adverse events

For Study **ENDV-01-002**, four adverse events were reported by three of the 21 subjects dosed. These included the following events (incidence): dizziness (1), headache (1), and hot flushes (2 separate events both in the same patient). All adverse events were rated as mild or moderate in severity.

One adverse event was considered by the investigator to be possibly treatment-related: headache. The remaining three adverse events were considered by the investigators to be unrelated to study medication.

For Study **GA 326**, frequent adverse events were evaluated by Dr. Gierhart in her NDA review in Table 26 (p.55) and Table 27 (p.56).

7.1.5.4 Common adverse event table

*Appears This Way
On Original*

Number (%) of Patients Reporting Adverse Events with $\geq 5\%$ Occurrence Rate by Body System

Body System/Adverse Events*	0.3 mg n=68	0.625 mg n=72	1.25 mg n=69	Placebo n=72
Number of Patients in Safety Sample (%)	68 (100)	72 (100)	69 (100)	72 (100)
Number of Patients with Adverse Events (%)	49 (72)	55 (76)	56 (81)	51 (71)
Number of Patients without Adverse Events (%)	19 (28)	17 (24)	13 (19)	21 (29)
Body as a Whole				
Abdominal Pain	3 (4)	11 (15)	3 (4)	7 (10)
Accidental Injury	6 (8)	2 (3)	3 (4)	5 (7)
Flu Syndrome	4 (6)	3 (4)	5 (7)	3 (4)
Headache	10 (15)	18 (25)	11 (16)	15 (21)
Pain	10 (15)	14 (19)	7 (10)	6 (8)
Digestive System				
Flatulence	3 (4)	5 (7)	3 (4)	2 (3)
Nausea	5 (7)	7 (10)	8 (12)	6 (8)
Nervous System				
Dizziness	5 (7)	3 (4)	1 (1)	3 (4)
Paresthesia	0	4 (6)	1 (1)	0
Respiratory System				
Bronchitis	0	3 (4)	5 (7)	3 (4)
Rhinitis	3 (4)	4 (6)	5 (7)	4 (6)
Sinusitis	2 (3)	3 (4)	5 (7)	2 (3)
Urogenital System				
Breast Pain	0	9 (12)	10 (14)	3 (4)
Dysmenorrhea	1 (2)	6 (8)	1 (1)	2 (3)
Vaginitis	1 (2)	5 (7)	2 (3)	3 (4)

*Treatment-emergent adverse events, regardless of relationship to study drug

7.1.5.5 Identifying common and drug-related adverse events

At least one treatment-emergent adverse event (i.e. an adverse event that occurred after the patient had taken at least one dose of study drug) was reported by 211 (75.1%) of the All Enrolled patient group. The frequency of treatment-emergent AE's increased slightly with increasing Enjuvia™ dose. As one progressed from placebo → 0.3mg → 0.625 mg → 1.25 mg the frequency of AE's increased from 70.8% (n=51) → 72.1% (n=49) → 76.4% (n=55) → 82.1% (n=56).

The treatment-emergent AE's reported by the greatest number of study subjects were headache, pain, and infection (bronchitis, rhinitis, sinusitis, flu-like syndrome, vaginitis).

7.1.5.6 Additional analyses and explorations

Selective exploration of individual adverse events for common adverse events was not performed, as the incidence of these common events was not dissimilar for comparable estrogen hormone therapy products already on the market.

7.1.6 Less Common Adverse Events

In general, a fairly large database is needed to evaluate less common adverse events and to identify relatively rare events of significant concern. Based on data from comparable estrogen hormone therapy products already on the market, further investigation to study the incidence of rare adverse events does not appear warranted at this time.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

During visit 1 (Screening), consent was obtained and the patient's eligibility for the Study **GA 326** was determined according to the inclusion and exclusion criteria after performing history, physical examination, vital signs, urinalysis, serum chemistry profile, complete fasting lipid profile, hormone profile (serum estradiol and FSH), and complete blood count with differential. These baseline laboratory tests were repeated at visit 5 (week 12) of Study **GA 326** as well as one month later (week 16).

The hematology tests included white blood cell (WBC) count with differential, red blood cell (RBC) count, hemoglobin, hematocrit, and platelet count.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Controlled comparisons provide the best data for deciding whether there is a signal of an effect of Enjuvia™ on a laboratory test. There does not appear to be any laboratory safety signal based on evaluation of data from either Study **ENDV-01-002** or Study **GA 326**.

7.1.7.3 Standard analyses and explorations of laboratory data

In situations where there is suspicion of a negative impact of the drug on patient laboratory values, three standard approaches to analysis of laboratory data are used. The first two analyses are based on comparative trial data, and the third focuses on all patients in the particular drug's phase 2-3 experience. Prior evaluation of Enjuvia's effect on laboratory values has not demonstrated any significant abnormalities, and comparative laboratory data among the different Enjuvia™ doses and placebo revealed no laboratory abnormalities which warranted further investigation.

7.1.7.3.1 Analyses focused on measures of central tendency

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

7.1.7.4 Additional analyses and explorations

There is no signal from the summary data to warrant additional analyses for dose-dependency, time-dependency, or drug-demographic, drug-disease, and drug-drug interactions. If variations in hormone levels are excluded, there was no pattern of clinically significant or unexpected changes in the serum chemistry, hematology, or urinalysis laboratory values noted for Enjuvia™

7.1.7.5 Special assessments

No special assessments concerning hepatotoxicity or nephrotoxicity were indicated for Enjuvia™.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

For the All Enrolled patient group, the temperature, respiratory rate, heart rate, blood pressure, and weight values summarized by visit and group were reviewed. At baseline, weight ranged from 78 to 323 lbs. For the heart rate values, no significant change in mean or median was noted across the visits. For systolic and diastolic blood pressure values, no significant changes in mean or median was noted across the visits.

Vital signs were measured at every study subject clinical visit in Study **GA 326**.

The observed changes in vital signs were as would be expected with drugs in the estrogen class.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

No overall Enjuvia™ versus placebo direct comparisons were made. As noted in 7.1.8.1, measurement of vital signs in study subjects was observational, not comparative.

7.1.8.3 Standard analyses and explorations of vital signs data

Observational analysis of vital signs data in Enjuvia™ study subjects was performed

7.1.8.3.1 Analyses focused on measures of central tendencies

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

7.1.8.4 Additional analyses and explorations

No additional analyses of vital signs data were performed.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

There were no ECG's obtained during any of the studies, either at baseline or during the course of the study.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

No overall Enjuvia™ versus placebo comparisons were made. As noted in 7.1.9.1, ECG testing was not performed.

7.1.9.3 Standard analyses and explorations of ECG data

No standard analyses and explorations of ECG testing were performed. As in noted in 7.1.9.1, ECG testing was not performed.

7.1.9.3.1 Analyses focused on measures of central tendency

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

7.1.9.4 Additional analyses and explorations

No additional analyses and explorations of ECG data were performed. As is noted in 7.1.9.1, ECG testing was not performed.

7.1.10 Immunogenicity

No human immunogenicity studies, data, or literature were submitted to this NDA on the topic.

7.1.11 Human Carcinogenicity

No human carcinogenicity studies were conducted under the IND for Enjuvia™. There were no data or literature submitted to this NDA on this topic. The approved label for Enjuvia™ 0.626 mg and 1.25 mg tablets, as well as other estrogen hormone therapy drugs, indicates that:

- Long-term continuous administration of estrogen has shown an increased risk of endometrial, breast, and ovarian cancer in humans.
- Long-term continuous administration of estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

7.1.12 Special Safety Studies

In some cases, special studies are warranted for concerns that arise such as QT interval abnormalities, or drugs that are intended to demonstrate a safety advantage over other, similar therapies. This is not the case with Enjuvia™, and no special studies are indicated.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No concerns about withdrawal phenomena or abuse potential have arisen from the studies conducted for this NDA, and no studies were conducted to assess these issues. FDA concurs that there is no need to examine this area any further at this time.

7.1.14 Human Reproduction and Pregnancy Data

No formal studies in humans on the effects of Enjuvia™ on human reproduction or pregnancy were performed. Similarly, no information on drug exposure on pregnant women, including any inadvertent exposure during drug development, was identified. Preclinical data failed to identify adverse fetal effects. Given that the indication for Enjuvia™ is for acute menopausal symptoms in women who are not capable of natural childbirth because of either age or surgical therapy, FDA concurs that there is no need to examine this area any further at this time.

In general, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of breast milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving estrogen. Caution should be exercised if Enjuvia™ is inadvertently administered to a post-partum or nursing woman.

7.1.15 Assessment of Effect on Growth

Enjuvia™ has not been tested in children under age 12 and is not indicated for pediatric patients. The approved label for Enjuvia™ states that the safety and efficacy of Enjuvia™ has not been established in pediatric patients.

7.1.16 Overdose Experience

There are no reports of overdosage of Enjuvia™.

In general, serious adverse effects have not been reported in young children following acute ingestion of large doses of estrogen-containing products. Overdosage of estrogen may cause nausea and vomiting, as well as abnormal uterine bleeding in females.

7.1.17 Postmarketing Experience

Enjuvia™ 0.625 mg and 1.25 mg tablets are currently marketed in the US for treatment of MSVMS associated with menopause. Examination of post-marketing data has been helpful for this NDA review.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The table of clinical studies that appears in Section 4.2 summarizes the clinical studies that were submitted to this NDA to support both safety and efficacy. Although only one of the two studies contained data that was used in the evaluation of efficacy, both of these studies collected safety data which was evaluated for the purposes of establishing the safety of Enjuvia™ tablets. As was discussed in Section 6.1.4, there was adequate demographic representation for postmenopausal women.

7.2.1.1 Study type and design/patient enumeration

Refer to Section 4.2 for the table that lists all clinical trials and summarizes the design features and number of subjects in each study.

7.2.1.2 Demographics

Baseline demographic characteristics for the 281 All Enrolled subjects in Study GA 326 were summarized in Table 9 on p.34 of Dr. Gierhart's review.

The majority of the All Enrolled patients were Caucasian (n=228, 81.1%). The second largest racial group was comprised of African-American patients (n=49, 17.4%), which the sponsor stated reflected the percentage of African-Americans in the US population. One patient checked only Hispanic as her race; however, 13 patients co-checked Caucasian and Hispanic and 3 checked African-American and Hispanic.

Mean treatment group age for All Enrolled patients ranged from 50.5 to 51.6 years, with individual ages ranging from 26 to 65 years and with an overall mean age of 51.1 years. Mean

treatment group weights for the four arms of All Enrolled patients ranged from 160.9 to 168.4 lbs., with individual weights ranging from 78 to 323 lb. and with an overall mean weight of 164 lb.

7.2.1.3 Extent of exposure (dose/duration)

There was only one dosing regimen used for all studies – one tablet once daily. In Study **GA 326** Enjuvia™ was taken continuously for 12 weeks.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Because Enjuvia™ was previously approved under an NDA, reporting of post marketing experience is mandated and all reports have been reviewed. No formal post-marketing study was required by FDA for previously approved Enjuvia™, however, so no additional clinical studies are cited in this review.

7.2.2.2 Postmarketing experience

Enjuvia™ 0.625 mg and 1.25 mg tablets are already marketed in the United States for the indications proposed in this NDA for the lower dose Enjuvia™ tablets. FDA's Adverse Events Reporting System (AERS) updates safety information on Enjuvia™ on a weekly basis. The most recent information available in AERS through the end of November 2004 has been cited in this review.

7.2.2.3 Literature

Recent publications in JAMA and the Obstetrics-Gynecology literature have extensively documented the potential risks and benefits of estrogen therapy for treatment of both acute (VMS, VVA) and chronic (prevention/treatment of osteoporosis) conditions associated with menopause. These publications have raised appropriate safety concerns about dose and duration of hormone therapy for menopausal symptoms, and have been appropriately highlighted in this NDA review.

7.2.3 Adequacy of Overall Clinical Experience

A total of 303 subjects were exposed to Enjuvia™ in all studies; 21 of these subjects were in a pharmacokinetics study (**ENDV-01-002**), and 281 subjects in a pivotal Phase 3, randomized, prospective, dose-ranging, double-blind study of 12 weeks duration (**GA 326**). These studies provided adequate safety and efficacy data to allow this reviewer to make a determination for approval of Enjuvia™ 0.3 mg and 0.45 mg tablets. Inclusion and exclusion criteria for study subjects' participation in **GA 326** were appropriate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Given the preclinical program conducted prior to Enjuvia's approval and the several years of human experience for the already approved doses of Enjuvia™, no additional preclinical testing or in vitro testing was necessary.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing of study subjects in the two clinical studies presented in this NDA, including efforts to monitor laboratory parameters, vital signs, and efforts to elicit adverse event data, was adequate. ECG data was not collected during the clinical trials, but there was no reason to collect this for an estrogen therapy product. Laboratory parameters were monitored at baseline, the 12 week endpoint of the study as well as one month after conclusion of the study; subjects were compared to their own baseline values and no cause for concern for patient safety was identified.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The clinical pharmacology of estrogen therapy products has been extensively investigated in the past. Metabolism and excretion is sufficiently understood to ease concern about safety problems in patients with impaired excretory or metabolic function as well as problems arising from drug-drug interactions.

Both in vitro and in vivo testing performed for other estrogen therapy products were adequate to identify the following: (1) the enzymatic pathways responsible for clearance of the drug and the effects of inhibition of those pathways, notably CYP450 enzymes; (2) the effect of the drug on CYP450 enzymes (inhibition, induction) and the effects of the drug on the PK of model compounds; and (3) the major potential safety consequences of drug-drug interactions. None of these issues raised concerns that mandated further testing of Enjuvia™.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

No recommendations for further study are being made by Barr Pharmaceuticals or DRUDP.

7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of the data submitted for conducting the safety review were sufficient to make the judgment that Enjuvia™ 0.3 mg and 0.45 mg tablets are safe to proceed to market. Adequate analysis and interpretation of safety results, including laboratory values, adverse event reporting, and pharmacokinetics have made for a thorough examination of Enjuvia™.

7.2.9 Additional Submissions, Including Safety Update

Additional safety information submissions to this NDA after the initial submission include the 4-month safety updates and weekly safety reports to AERS (Adverse Event Reporting System). There is no additional clinical trial safety information to report since no additional trials have been done since the original NDA submission. No new safety signals concerning Enjuvia™ have appeared from this information.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The incidence of serious adverse events in Study **GA 326** and Study **ENDV-01-002** was low, and of the 5 total adverse events only 2 (cholecystitis at 0.3 mg dose, cerebrovascular accident at 0.625 mg dose) were potentially drug-related. No definitive statement regarding causality may be made.

The incidence of non-serious adverse events was low, and spread relatively evenly among the different doses of Enjuvia™ and placebo. Inclusion in the label of a chart that provides this information is sufficient.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

There were only two clinical studies –**GA 326** and **ENDV-01-002** – used to support the safety and efficacy claims for this NDA. Safety data were examined individually for each study and as pooled data. Given that only **GA 326** was a pivotal clinical study and had a much greater number of patients (281 vs. 21), the bulk of the safety data was derived from Study **GA 326**.

7.4.1.2 Combining data

All safety data were pooled to increase the likelihood of uncovering adverse events that occur with low frequency or are rare.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The incidence of all adverse events increased slightly in Study **GA 326** as dose of Enjuvia™ increased, but there was no direct correlation between increasing dose of Enjuvia™ and an increase in the incidence of serious adverse events.

7.4.2.2 Explorations for time dependency for adverse findings

Enjuvia™ is taken daily on a continuous basis. No exploration for time-dependent adverse findings was undertaken. Based on the available literature for estrogen therapy from the Women's Health Initiative studies published in JAMA and referenced in Sections 1.1 and 2.4 of this review, the risk of cardiovascular and neoplastic morbidity does appear to increase with longer use of estrogen therapy. This finding underscores DRUDP's recommendation that products such as Enjuvia™ should be taken in the lowest effective dose for the shortest duration of time necessary when used to treat acute menopausal symptoms such as hot flashes.

7.4.2.3 Explorations for drug-demographic interactions

The effectiveness and safety of Enjuvia™ was explored to the extent possible in race. No exploration of gender or age was carried out since Enjuvia™ is intended for use only by menopausal women. There was no apparent safety or efficacy concern for Enjuvia™ based on race.

7.4.2.4 Explorations for drug-disease interactions

There was no evidence of unexpected drug-disease interaction.

7.4.2.5 Explorations for drug-drug interactions

There was no evidence of drug-drug interaction.

7.4.3 Causality Determination

Although determining an association of certain safety events with a drug may be straightforward, establishing causality is not. The mere juxtaposition of two events may imply, but does not establish, cause and effect. (David Hume. Treatise on Human Nature 1739).

Fortunately, in the case of Enjuvia™ only a small number of AE's reported were serious and none occurred with a high incidence. Of the five serious adverse events reported for Study **GA 326**, only two (one episode of cholecystitis and one cerebrovascular accident) could remotely be construed to be either directly or indirectly related to use of Enjuvia™; the sponsor believed these two SAE's were not directly drug-related whereas Dr. Gierhart determined that they might

have been. Based on the existing literature on hormone therapy for acute menopausal symptoms, both cholecystitis and stroke are recognized potential morbidities for hormone therapy products. Thus, whether directly related or not, the incidence of these SAE's in the pivotal clinical study was well within acceptable limits, and there is no signal for these events due to Enjuvia™ use.

In terms of more frequent but non-serious adverse events (e.g. nausea, flatulence, flu-like syndrome), the incidence in both the treatment and placebo groups was comparable.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Enjuvia™ 0.3 and 0.45 mg tablets are the only doses of Enjuvia™ proposed for this NDA. The dosing regimen is one tablet daily. This dosing regimen is identical to that for the higher doses of Enjuvia™. No other dosing schedule is recommended. It is recommended that Enjuvia™ tablets be taken each day at about the same time. If one days dose is missed, it is not recommended that two doses be taken at the same time. DRUDP recommends that women taking Enjuvia™ for MSVMS associated with menopause start at the lowest effective dose, and consult frequently with their health care provider to discuss how well that dose is working. DRUDP also recommends that, in general, estrogens for acute conditions such as VMS and VVA should be taken only as long as needed.

8.2 Drug-Drug Interactions

No new drug-drug interactions were uncovered during the review process. In vitro and in vivo studies have shown that estrogens are metabolized partially by the cytochrome P450 3A4 (CYP3A4). Therefore, inducers (St. John's Wart, phenobarbital, carbamazepine, rifampin) may reduce plasma concentrations of Enjuvia™ and thus possibly result in a decrease in therapeutic effects and/or result in abnormal uterine bleeding. Similarly, inhibitors of CYP3A4 (e.g. erythromycin, clarithromycin, ketokonazole, itraconazole, ritonavir, grapefruit juice) may increase plasma concentrations of Enjuvia™ and result in untoward side effects as well.

8.3 Special Populations

Enjuvia™ was investigated in postmenopausal women aged 26-65 years. No pharmacokinetic studies were conducted in other special populations, including patients with renal or hepatic impairment. Patients with renal insufficiency are not restricted in their use of Enjuvia™, but use of the drug in patients with hepatic insufficiency is contraindicated and is noted in the current label.

Based on data from comparable hormone therapy products, no formal studies in humans on the effects of drugs on reproduction or pregnancy were performed; similarly, no information on drug exposure in pregnant women, including any inadvertent exposure during drug development, was identified. Because Enjuvia™ is intended for use in postmenopausal women, no formal study on

reproductive function or pregnancy is indicated. Enjuvia™ is not intended for use in either children or pregnant women.

There have not been sufficient numbers of geriatric patients involved in studies utilizing Enjuvia™ to determine whether those over 65 years of age differ from younger subjects in their response to Enjuvia™.

8.4 Pediatrics

Enjuvia™ 0.3 mg and 0.45 mg tablets for MSVMS associated with menopause essentially preclude a pediatric indication or need for pediatric testing.

8.5 Advisory Committee Meeting

There were no recent advisory committee meetings in which Enjuvia™ or similar estrogen hormone therapy product was directly discussed. Tangential reference to estrogen and estrogen-progestogen therapy for acute versus chronic menopausal conditions was made during the Endocrine and Metabolic Drugs Advisory Committee Meeting of October 7, 2003 (Holiday Inn, Bethesda, Maryland).

8.6 Literature Review

Literature relevant to the NDA has been referenced throughout the review as needed. Most of the pertinent literature appears in Section 1.1 and 2.2 respectively. There is no need for a separate comprehensive review of the literature.

8.7 Post marketing Risk Management Plan

There is no need for a post marketing risk management plan.

8.8 Other Relevant Materials

All other relevant materials are included in the relevant section of the review. Relevant journal articles, such as those from the Women's Health Initiative which appeared in the Journal of the American Medical Association (JAMA), are cited where appropriate.

9 OVERALL ASSESSMENT

9.1 Conclusions

Enjuvia™ 0.3 mg is safe and effective for the treatment of MSVMS associated with menopause.

A statistically significant decrease in mean frequency and severity of baseline MSVMS when compared to placebo after 4 and 12 weeks of continuous use was demonstrated.

Enjuvia™ 0.3 mg tablets have also been shown to be safe for its intended use as recommended in the labeling by all tests reasonably applicable to the assessment of safety. These include comparison of adverse events in the clinical trials between groups, reviewing laboratory data, reviewing post marketing and reports from already marketed Enjuvia™ products. Demographic data allowed adequate evaluation of safety and efficacy in subgroups based on race. Sufficient data have been submitted and reviewed to provide adequate directions for use, including data that describe a safe and effective dose. The drug is not indicated for use in any pediatric population.

9.2 Recommendation on Regulatory Action

This new drug application for Enjuvia™ 0.3 mg is recommended for approval for treatment of post-menopausal vasomotor symptoms (“hot flushes”). Because of bracketing of the 0.45 mg dose between the already approved 0.625 mg dose and the recommended for approval 0.3 mg dose, the 0.45 mg dose is also recommended for approval for treatment of post-menopausal vasomotor symptoms.

No phase 4 commitments will be required. The sponsor’s proposed labeling as submitted in the NDA requires revision before approval.

9.3 Recommendation on Post marketing Actions

There are no recommendations for post marketing actions.

9.3.1 Risk Management Activity

There are no recommended post marketing risk management activities.

9.3.2 Required Phase 4 Commitments

There are no required Phase 4 commitments.

9.3.3 Other Phase 4 Requests

DRUDP is interested in acquisition of further data from the sponsor concerning the dose titration issue, i.e. how many of patients currently taking the already approved higher (0.625, 1.25 mg) doses of Enjuvia™ tablets for VMS may be successfully switched to the lowest 0.3 mg dose.

9.4 Labeling Review

The appendix to this review includes a line-by-line review of the sponsor’s proposed label, with appropriate markings for every suggested addition and deletion to that text. In the remainder of

Clinical Review
{Insert Reviewer Name}
{Insert Application and Submission Number}
{Insert Product Trade and Generic Name}

this section, a summary of the major changes needed in the sponsor's proposed labeling is presented. Refer to the appendix for a line-by-line review.

9.5 Comments to Applicant

After completing internal team discussion of the sponsor's proposed label, comments from DRUDP have been incorporated into the label that follows.

**Appears This Way
On Original**

10 APPENDICES

10.1 Review of Individual Study Reports

Highlights of relevant individual studies were discussed in the body of this review. No further review of individual study reports is warranted.

10.2 Line-by-Line Labeling Review

In this section, two sets of the label will be provided. The first label is the sponsor's proposed label (Section 10.2.1). The second label is DRUDP's revised label (Section 10.2.2).

48 Page(s) Withheld

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

✓ § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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/s/

Bruce Patsner
12/20/04 02:35:01 PM
MEDICAL OFFICER

Daniel A. Shames
12/20/04 02:39:57 PM
MEDICAL OFFICER

Enjuvia™ Team Leader Review

NDA: 21-443/ 21-609
Drug: Enjuvia™

Proposed Indications: Treatment of moderate-to-severe vasomotor symptoms

Dosage/Form/Route: 0.30 mg synthetic conjugated estrogens, B
0.45mg synthetic conjugated estrogens, B
0.625 mg synthetic conjugated estrogens, B
1.25 mg synthetic conjugated estrogens, B

Applicant: Endeavor Pharmaceuticals

Original Submission Date: March 21, 2002
Receipt Date: March 22, 2002
Primary Review Completed: March 28, 2003
Date of Memorandum: April 22, 2003

Background

The Agency has previously approved 4 drug products that contain conjugated estrogens, Premarin®, Prempro™, Premphase® and Cenestin®.

Premarin® (1.25 mg conjugated estrogens) was approved in 1942 for the relief of vasomotor symptoms. Premarin® contains a mixture of the estrogens sodium estrone sulfate and sodium equilin sulfate with concomitant components, as sodium sulfate conjugates, 17 α -dihydroequilin, 17 α -estradiol, and 17 β -dihydroequilin.

In 1972, the Federal Register Drug Efficacy Study Implementation Notice (DESI 1543: 37 FR 14826 dated July 25, 1972) which was based on the National Academy of Sciences-National Research Council Drug Efficacy Study Group (NAS-NRC) review of published literature, found non-contraceptive estrogen drugs (including Premarin®) to be effective for several "DESI Indications." This 1972 notice and two additional notices (DESI 1543: 41 FR 43114 dated September 29, 1976 and 51 FR 12568 dated April 11, 1986 defined these DESI Indications" as follows:

1. moderate-to-severe vasomotor symptom (MSVMS) associated with the menopause;
2. senile vaginitis;
3. kraurosis vulvae;
4. pruritis vulvae;
5. abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology;
6. female hypogonadism;
7. amenorrhea;
8. female castration;
9. primary ovarian failure;
10. prevention of postpartum breast engorgement;

11. palliation of selected cases of inoperable progressing mammary and prostatic carcinoma; and
12. postmenopausal osteoporosis.

On September 29, 1976, Federal Register notice 41 FR 43108 instituted “class labeling for estrogen products. The purpose was to introduce uniform labeling with respect to benefits and risks of these products.

Wyeth-Ayerst received approval for NDA 20-303 on December 30, 1994 to market Prempro™ and Premphase®, two oral combination drug products consisting of conjugated estrogens (CE) and medroxyprogesterone acetate (MPA). Two dosage regimens were approved, Prempro™2.5 (0.625 mg CE/2.5 mg MPA) and Premphase (0.625 mg CE/ 5mg MPA). Initially, Prempro™2.5 and Premphase® were each co-packaged products. Prempro™ consisted of one tablet of CE and one tablet of MPA taken on a continuous daily basis and Premphase® consisted of one tablet of CE taken on days 1-14 of the month and one tablet of CE and one tablet of MPA taken on days 15-28 of the month. On November 17, 1995, the Agency approved NDA 20-527 for Prempro™ 2.5, a single tablet of 0.625 mg CE/2.5 mg MPA taken on a continuous daily basis and Premphase®, a single tablet of CE taken for days 1-14 of the month and single tablet of 0.625 mg CE/2.5 mg MPA taken for days 15-28 of the month. NDA 20-527, supplement 006 for Prempro™ 5 (0.625 mg CE/5 mg MPA in a single tablet taken on a continuous daily basis) was approved on January 9, 1998. Prempro™ 2.5, Prempro™ 5, and Premphase® are all approved for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause (VMS) in women with a uterus, treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy associated with the menopause (VVA) in women with a uterus, and prevention of postmenopausal osteoporosis.

Cenestin® (synthetic conjugated estrogens, A) was approved on March 27, 1999 for the treatment of moderate-to-severe vasomotor symptoms (MSVMS) associated with the menopause. It is an oral drug product, administered in tablet form, that contains the following nine estrogenic substances in combination: sodium estrone sulfate, sodium equilin sulfate and sodium 17 α -dihydroequilin sulfate, sodium 17 α -estradiol sulfate, sodium 17 β -dihydroequilin sulfate, sodium 17 α -dihydroequilenin sulfate, 17 β -dihydroequilenin sulfate, sodium equilenin sulfate and sodium 17 β -estradiol sulfate. Three dosage strengths of Cenestin® (0.625 mg, 0.9 mg, and 1.25 mg) are approved for the treatment of MSVMS associated with the menopause. On June 17 2002, the Agency approved Cenestin® 0.3 mg for the treatment of vulvar and vaginal atrophy.

On September 22, 1999, draft revision of the LABELING GUIDANCE FOR NON-CONTRACEPTIVE ESTROGEN DRUG PRODUCTS- PRESCRIBING INFORMATION FOR HEALTH CARE PROVIDERS AND PATIENT LABELING was noticed in 64 FR number 186. This Labeling Guidance specified that indications for estrogen and estrogen/progestin drug products would not be granted based on “class labeling” and would be given based on clinical trial demonstration of efficacy.

The 1999 Draft Labeling Guidance was withdrawn on September 10, 2002 for review and revision following the publication of the results of the National Institutes of Health Women’s Health Initiative trial. On February 3, 2003, a revised Draft Guidance for Industry, “Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Prescribing Information for Health Care Providers and Patient Labeling” was published in the Federal Register [68 FR 5300].

1 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

Withheld Track Number: Medical- 2

A pre-NDA Clinical, Statistical, and Biopharmaceuticals teleconference was held with the sponsor on February 21, 2002.

A full waiver to the requirement to assess the safety and effectiveness of Enjuvia in pediatrics was submitted on February 25, 2002 and was granted in a regulatory letter dated March 18, 2002. On March 18, 2002 the Sponsor submitted their pre-NDA meeting minutes. The Sponsor objected to Enjuvia's chemical name being designated "synthetic conjugated estrogens, B" since they believe that the use of "B" with Enjuvia gives Cenestin (synthetic conjugated estrogens, A) an unfair advantage and may cause confusion. The Sponsor also wished to include in the minutes the comparison they wished to raise of their GA326 study to the Cenestin study conducted to obtain approval for the treatment of vasomotor symptoms. During the pre-NDA meeting the Division had informed the sponsor that no discussion of the Cenestin study conducted to obtain approval for the treatment of vasomotor symptoms would be held during the meeting.

NDA 21-443 was submitted on March 21, 2002 (received March 22, 2002) and was administratively filed on May 21, 2002.

Clinical

Study GA 236 was a randomized, double blind, placebo-controlled, multi-center (22 centers) study conducted in the U.S. The efficacy analyses for those subjects meeting the requisite number of moderate-to-severe vasomotor symptoms (MSVS) are presented in Tables 1 and 2 which are modified from the medical officer's (MO) Tables 2 and 3.

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Table 1: Mean Weekly Number of Moderate-to-Severe Hot Flushes and Change from Baseline in Mean Weekly Number of Moderate-to-Severe Hot Flushes during Therapy in All Subjects with \geq 7 Moderate-to-Severe Hot Flushes Per Day at Baseline, Intent-to-Treat Population with Last Observation Carried Forward (LOCF)^a

Week	0.3 mg	0.625 mg	1.25 mg	Placebo
Baseline Mean Number (SD)	104.3 (57.7)	97.3 (82.1)	86.8 (42.1)	96.4 (58.2)
Week 4 Mean Number LSMean Change ^b p-value vs. placebo ^c	47.0 (52.9) -49.8 (5.2) 0.0821	23.3 (26.9) -72.8 (5.0) <0.0001	24.6 (47.0) -68.3 (5.1) <0.0001	57.8 (47.5) -37.2 (5.0)
Week 8 Mean Number LSMean Change ^b p-value vs. placebo ^c	34.8 (50.8) -61.8 (4.6) 0.0136	13.0 (17.8) -83.0 (4.4) <0.0001	13.8 (27.3) -80.2 (4.5) <0.0001	49.5 (47.9) -45.9 (4.5)
Week 12 Mean Number LSMean Change ^b p-value vs. placebo ^c	30.7 (47.7) -66.3 (4.6) 0.0051	12.2 (18.7) -84.6 (4.4) <0.0001	12.4 (26.3) -82.6 (4.5) <0.0001	47.5 (49.8) -48.3 (4.5)

^aLOCF = last observation carried forward

^bLSMean change = Least Square Mean change from baseline

^cp-value is based on analysis of covariance with treatment as factor and baseline as covariate

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Table 2. Mean Weekly Severity and Change from Baseline in the Mean Daily Severity of Hot Flushes during Therapy in All Subjects with ≥ 7 Moderate-to-Severe Hot Flushes Per Day at Baseline, Intent-to-Treat Population with LOCF^a

Week	0.3 mg	0.625 mg	1.25 mg	Placebo
Baseline				
Mean Severity	2.3 (0.4)	2.4 (0.3)	2.4 (0.4)	2.4 (0.4)
Week 4				
Mean Severity	1.9 (0.6)	1.7 (0.9)	1.4 (1.0)	2.1 (0.8)
LSMean Change ^b	-0.5 (0.1)	-0.7 (0.1)	-1.0 (0.1)	-0.3 (0.1)
p-value vs. placebo ^c	0.3105	0.0092	<0.0001	
Week 8				
Mean Severity	1.6 (0.9)	1.4 (1.0)	1.0 (1.0)	1.9 (0.9)
LSMean Change ^b	-0.8 (0.1)	-1.0 (0.1)	-1.4 (0.1)	-0.5 (0.1)
p-value vs. placebo ^c	0.0606	0.0007	<0.0001	
Week 12				
Mean Severity	1.5 (1.0)	1.1 (1.1)	1.0 (1.0)	1.9
LSMean Change ^b	-0.9 (0.1)	-1.3 (0.1)	-1.4 (0.1)	-0.5 (0.1)
p-value vs. placebo ^c	0.0181	<0.0001		<0.0001

^aLOCF = last observation carried forward

^bLSMean change = Least Square Mean change from baseline

^cp-value is based on analysis of covariance with treatment as factor and baseline as covariate

For estrogen alone products intended to treat moderate to severe vasomotor symptoms, efficacy is demonstrated when the primary efficacy analyses show a clinically and a statistically significant reduction, which occurs by 4 weeks of initiation of treatment and is maintained throughout 12 weeks of treatment, in both the frequency and severity of hot flushes in the treated groups compared with the control groups. The 0.625 mg and the 1.25 mg CE10 dosage groups show a statistically significant reduction in MSVMS (both frequency and severity) when compared to placebo at Week 4 and Week 12. There is a decrease of greater than 2 moderate-to-severe hot flushes per day in the 0.625 mg CE10 dosage group and the 1.25 mg CE10 dosage group compared to placebo that is evident at Week 4 and maintained through Week 12.

The 0.3 mg CE10 dosage group did not reach statistical significance compared to placebo for frequency or severity at Week 4. At Week 8 statistical significance for this group compared to placebo was seen in frequency and not severity. At Week 12, the 0.3 mg CE10 dosage group did demonstrate statistically significant reduction compared to placebo for both frequency and severity.

In addition to the analyses shown above, the Statistical reviewer also performed subgroup analysis of VMS by age in those subjects who completed 12 weeks of treatment. The studies were not prospectively powered to demonstrate efficacy in these subgroups and the results are considered observational only. The results by age group (<50, 50-59, ≥ 60) showed that in women < 50, the 0.3 mg CE10 dosage strength did not demonstrate efficacy in the treatment of MSVMS. The 0.625 mg CE10 dosage strength demonstrated a statistically significant treatment effect on vasomotor symptom frequency at Weeks 4, 8, and 12, but on severity only at Week 12. The 1.25 mg CE10 dosage strength demonstrated a statistically significant treatment effect at Weeks 4, 8 and 12 on both frequency and severity.

In the 50 – 59 age group all CE10 dosage strengths demonstrated a statistically significant treatment effect on both frequency and severity at Weeks 4, 8 and 12

For the > 59 age group, no statistically significant reduction in the frequency or in the severity of MSVMS were observed for any 3 of the active treatment groups.

No deaths were reported during Study GA326. Five subjects experienced a total of 8 serious adverse events. There was one case of cerebrovascular accident/hemorrhagic stroke and 1 case of cholecystitis. There were cases of benign breast disease but no cases of breast cancer.

Division of Scientific Investigations (DSI) Report

Four clinical sites were investigated for compliance with good clinical practice. These included Philip Ponder, M.D. in Winston-Salem, N.C., John Lenihan, Jr., M.D. in Tacoma, W.A., Eugene Eisenman, M.D., in Las Vegas, NV and Gita P. Gidwani, M.D. in Cleveland, OH. All sites were given either NAI or VAI and found to be acceptable.

Clinical Pharmacology and Biopharmaceutics

In support of this application, the Sponsor has submitted to the human pharmacokinetics and bioavailability section of the NDA, one fasting single dose PK study (END-01-002) with 2 x 0.625 mg CE10. In addition, four BE studies between their previous CE 9 formulation (similar to Enjuvia, but minus the 10th component) and Premarin at two dose levels (2x0.625 mg and 1.25 mg) under fasting as well as fed conditions were also submitted. To support a second manufacturing site and the 0.45 mg dose (for which no clinical trial data was submitted), the Sponsor submitted In Vitro and In Vivo Correlation (IVIVC). The IVIVC was developed using in vivo data from one PK study with the CE 10 formulation and the four BE studies with the CE 9 formulation. Also in support of the second manufacturing site, the sponsor has collected additional PK information at that site

END-01-002, the single dose PK study, showed that the conjugated estrogens, estrone sulfate and equilin sulfate are slowly absorbed and reach peak concentration between 7 to 10 hours following oral administration and decline slowly with a terminal half life ranging from 11 to 23 hours. No multiple dose PK information was submitted with this application. The Sponsor is currently conducting a multiple dose PK study.

The food effect studies showed that food did not affect the pharmacokinetics of the 9-component CE formulation. Therefore, food is unlikely to affect the PK of Enjuvia.

Upon review, the IVIVC was not acceptable. However, in an amendment dated January 17, 2003, the Sponsor submitted pharmacokinetic data on the 0.625 mg and the 0.45 mg tablets manufactured at the second site, _____ . This data was sufficient for acceptance of the — site.

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB DPEII) finds the information submitted in the NDA to be acceptable.

From chemistry, manufacturing, and controls point of view, the NDA may be approved pending acceptable labeling.

The tradename was found acceptable by in reviews dated June 24 2002, September 24, 2002 and December 11, 2002.

Conclusions and Recommendations

The 0.625 mg and 1.25 mg dosage strength of Enjuvia were found in Study GA-236 to be effective in the treatment of moderate to severe vasomotor symptoms. The 0.3 mg dose was found to be ineffective in the treatment of moderate to severe vasomotor symptoms in this trial. No data was submitted to assess the effectiveness of the 0.45 mg dose, as the Sponsor intended to seek this dosage strength based on bracketing between the 0.3 mg dose and the 0.625 mg doses if these were to be approved. I agree with primary Medical Officer that the 0.625 mg and 1.25 mg dosage strengths can be approved. The 0.3 mg and 0.45 mg dosage strengths can not be approved on the basis of the information submitted. The Sponsor will be advised that if they want to pursue the indication of treatment of moderate to severe vasomotor symptoms for the 0.3 mg and 0.45 mg dosage strengths that new clinical trial data demonstrating efficacy will be necessary.

On the basis of additional Pharmacokinetic data collected at the second site of manufacturing, — it has been determined that this site is acceptable.

Recommendations for changes to the labeling were sent to the Sponsor on April 17, 2003. The revisions included removal of reference to 0.3 mg and 0.45 mg dosage strength tablets. Additional recommendations for revisions were consistent with the 2003 Draft Guidance For Industry, entitled “Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Prescribing Information for Health Care Providers and Patient Labeling.” The Sponsor has not sent a reply accepting any of these revisions.

I recommend that the 0.625 mg and 1.25 mg dosage strengths receive an approvable action pending acceptance of labeling recommendations and the 0.3 mg and 0.45 mg dosage strengths receive a non-approvable action. The NDA was administratively split in order to take two separate actions. The 0.625 mg and 1.25 mg dosage strengths were retained under NDA 21-443 and the 0.3 mg and 0.45 mg will receive an action under NDA 21-609.

Shelley R. Slaughter, MD, Ph.D.
Medical Officer Team Leader

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/s/

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