21310

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 21-310

Trade Name Alora

Generic Name Estradiol Transdermal System

Sponsor Watson Laboratories, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NDA 21-310

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	Included
Approval Letter	✓
Tenative Approval Letter	—
Approvable Letter	✓
Final Printed Labeling	✓
Medical Review(s)	✓
Chemistry Review(s)	✓
EA/FONSI	—
Pharmacology Review(s)	
Statistical Review(s)	✓
Microbiology Review(s)	—
Clinical Pharmacology Biopharmaceutics Review(s)	✓
Bioequivalence Review(s)	✓
Administrative Document(s)	
Correspondence	✓

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-310

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-310

Watson Laboratories, Inc.
Attention: Dorothy A. Frank, M.S., R.A.C.
Executive Director, Proprietary Regulatory Affairs
417 Wakara Way
Salt Lake City, UT 84108

Dear Ms. Frank:

Please refer to your new drug application (NDA) dated January 12, 2001, received January 16, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alora (estradiol transdermal system) 0.025 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day.

Your submission of February 5, 2002, constituted a complete response to our January 18, 2002, action letter.

This new drug application provides for 1) addition of a 0.025 mg/day strength product and 2) addition of an indication for the prevention of postmenopausal osteoporosis for all strengths.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert) and submitted draft labeling (pouch and carton labels submitted on November 15, 2001). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-310." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA, NDA 20-655, for this drug product, not to this NDA. In the future, do not make submissions to this NDA except for the final printed labeling requested above.

If you have any questions, call Samuel Y. Wu, Pharm.D., Regulatory Project Manager, at 301-827-6416.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

David Orloff
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-310

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-310

NOV 16 2001

Watson Laboratories, Inc.
Attention: Dorothy A. Frank, M.S., R.A.C.
Director, Regulatory Affairs
Research Park
417 Wakara Way
Salt Lake City, UT 84108

Dear Ms. Frank:

Please refer to your new drug application (NDA) dated January 12, 2001, received January 16, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alora (estradiol transdermal system) 0.025 mg/day, 0.05 mg/day, and 0.075 mg/day.

We acknowledge receipt of your submissions dated February 14, May 11, September 26, October 16 and 19, and November 7, 2001.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert, text for the patient package insert). In addition, submit a copy of your proposed container and pouch label.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

If you have any questions, call Samuel Y. Wu, Pharm.D., Regulatory Project Manager, at 301-827-6416.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
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Labeling

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/s/

David Orloff
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-310

Watson Laboratories, Inc.
Attention: Dorothy Frank, M.S., R.A.C.
Director, Regulatory Affairs
Research Park
417 Wakara Way
Salt Lake City, UT 84108

JAN 18 2002

Dear Ms. Frank:

Please refer to your new drug application (NDA) dated January 12, 2001, received January 16, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alora (estradiol transdermal system) 0.02 5mg/day, 0.05 mg/day, and 0.075 mg/day.

We acknowledge receipt of your submissions dated January 14 and 16, 2002. Your submission of November 19, 2001, constituted a complete response to our November 16, 2001, action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following labeling issues:

1. The table regarding vasomotor symptoms cannot be verified. To support Table 3, "Mean Change from Baseline in Frequency of Moderate-to-Severe Vasomotor Symptoms for **Alora** Compared to Placebo," submit the efficacy data from the placebo-controlled clinical trial (E94001). These data should be provided in SAS transport format according to the Guidance for Industry, entitled, "Providing Regulatory Submissions in Electronic Format-NDAs." Data should include values at baseline and weeks 4, 8 and 12, utilizing the last observation carried forward (LOCF) data imputation method. A data flag should be used to indicate any imputed value.

2. The graph provided by the Agency in figure 3 is an example of the presentation requested for that figure, "Mean % change in BMD from baseline at 1 and 2 years after initiation of therapy with placebo and Alora 0.025. 0.05 and 0.075 mg/day." A new graph using the corrected numbers in the completer and ITT populations should be generated.

In addition, it will be necessary for you to submit draft labeling for the drug. Revisions have been incorporated directly into the enclosed labeling (text for the package insert, text for the patient package insert). Additions have been noted with underlining, deletions have been noted as ~~strikeouts~~. Additional comments requiring response are in **14 pt bold face type.**

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Samuel Y. Wu, Pharm.D., Regulatory Project Manager, at 301-827-6416.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

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

/s/

Mary Parks
1/18/02 04:41:09 PM
for Dr. Orloff

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Draft

Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-310

FINAL PRINTED LABELING

Estradiol Matrix
Transdermal Delivery System
NDA 21-310

Package Insert

APPEARS THIS WAY
ON ORIGINAL

Watson Laboratories Inc.
Research Park
417 Wakara Way
Salt Lake City, UT 84108 USA

Alora®
(estradiol transdermal system)
Continuous Delivery for Twice Weekly Dosing

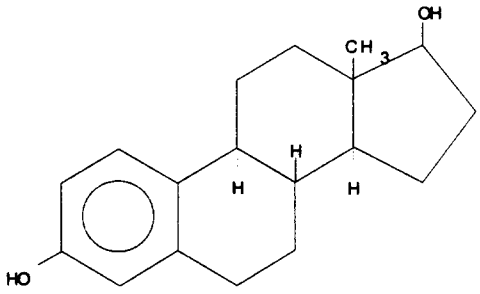
PRESCRIBING INFORMATION

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER.

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is currently no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose.

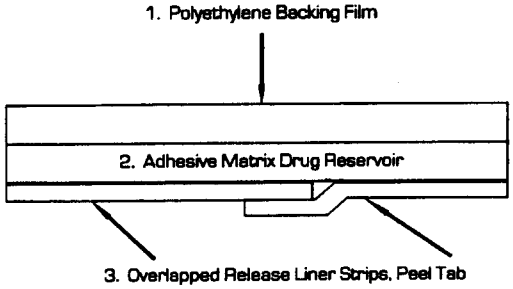
DESCRIPTION

Alora (estradiol transdermal system) is designed to deliver estradiol continuously and consistently over a 3 or 4-day interval upon application to intact skin. Four strengths of **Alora** are available, having nominal *in vivo* delivery rates of 0.025, 0.05, 0.075, and 0.1 mg estradiol per day through skin of average permeability (inter-individual variation in skin permeability is approximately 20%). **Alora** has contact surface areas of 9, 18, 27, and 36 cm^2 and contains 0.75, 1.5, 2.3, and 3.0 mg of estradiol, USP, respectively. The composition of the estradiol transdermal systems per unit area is identical. Estradiol, USP is a white, crystalline powder that is chemically described as estra-1,3,5(10)-triene-3, 17ß-diol, has an empirical formula of $C_{18}H_{24}O_2$ and has molecular weight of 272.39. The structural formula is:



Estradiol

Alora consists of three layers. Proceeding from the polyethylene backing film as shown in the cross-sectional view below, the adhesive matrix drug reservoir that is in contact with the skin consists of estradiol, USP and sorbitan monooleate dissolved in an acrylic adhesive matrix. The polyester overlapped release liner protects the adhesive matrix during storage and is removed prior to application of the system to the skin.



CLINICAL PHARMACOLOGY

Estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 μg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue. Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism. Estrogen replacement therapy acts to reduce the elevated levels of these hormones seen in postmenopausal women.

Pharmacokinetics

The skin metabolizes estradiol only to a small extent. In contrast, orally administered estradiol is rapidly metabolized by the liver to estrone and its conjugates, giving rise to higher circulating levels of estrone than estradiol. Therefore, transdermal administration produces therapeutic plasma levels of estradiol with lower levels of estrone and estrone conjugates and requires smaller total doses than does oral therapy.

Absorption

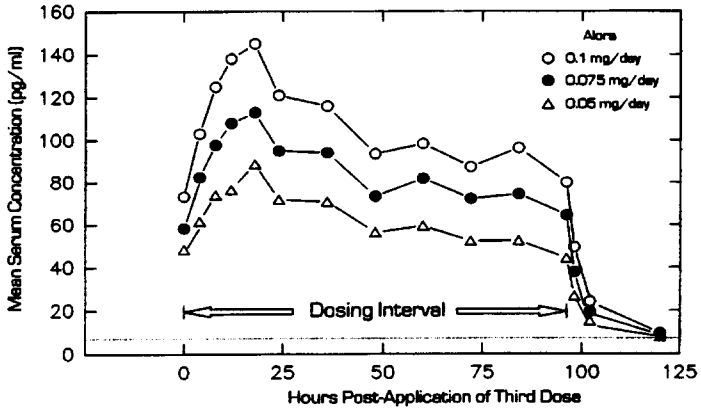
Estradiol is transported across intact skin and into the systemic circulation by a passive diffusion process, the rate of diffusion across the stratum corneum being the principal factor. **Alora** presents sufficient concentration of estradiol to the surface of the skin to maintain continuous transport over the 3 to 4 day dosing interval.

Direct measurement of total absorbed dose of estradiol through analysis of residual estradiol content of systems worn over a continuous four day interval during 251 separate occasions in 123 postmenopausal women demonstrated that the average daily dose absorbed from **Alora** was 0.003 ± 0.001 mg estradiol per cm^2 active surface area. The nominal mean *in vivo* daily delivery rates of estradiol calculated from these data are 0.027 mg/day, 0.054 mg/day, 0.081 mg/day, and 0.11 mg/day for the 9 cm^2, 18 cm^2, 27 cm^2, and 36 cm^2 **Alora**, respectively.

In another study, 20 women also were treated with three consecutive doses of **Alora** 0.05 mg/day, **Alora** 0.075 mg/day and **Alora** 0.1 mg/day on abdominal application sites. Mean steady state estradiol serum concentrations observed over the dosing interval are shown in Figure 1.

Figure 1

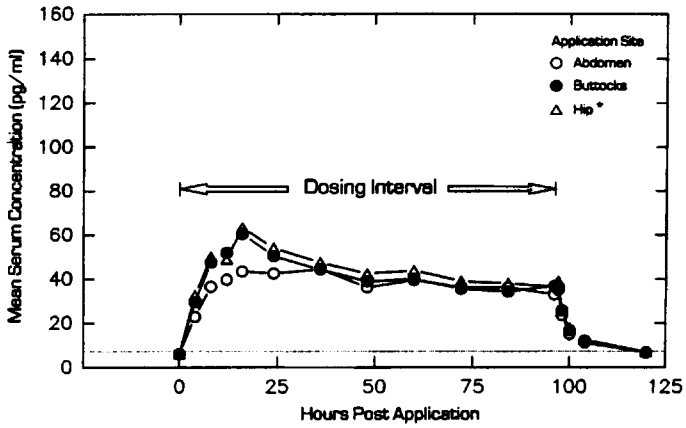
Mean steady state estradiol serum concentration during the third twice weekly dose of **Alora** 0.1 mg/day, **Alora** 0.075 mg/day, and **Alora** 0.05 mg/day in 20 postmenopausal women.



In a single dose randomized crossover study conducted to compare the effect of site of **Alora** application, 31 postmenopausal women wore single **Alora** 0.05 mg/day for four day periods on the lower abdomen, upper quadrant of the buttocks, and outside aspect of the hip. The estradiol serum concentration profiles are shown in Figure 2.

Figure 2

Mean estradiol serum concentrations during a single 4-day wearing of **Alora** 0.05 mg/day applied by 31 postmenopausal women to the lower abdomen, upper quadrant of the buttocks or outer aspect of the hip.



*C_{max} and C_{avg} statistically different from abdomen

Table 1 provides a summary of the estradiol pharmacokinetic parameters studied during biopharmaceutic evaluation of **Alora**.

Table 1

Mean (SD) Pharmacokinetic Profile of **Alora** Over an 84-Hour Dosing Interval

Alora (mg/day)	Application Site	N	Dosing	C_{max} (pg/ml)	C_{min} (pg/ml)	C_{avg} (pg/ml)	CL (L/hr)
0.05	Abdomen	20	Multiple	92 (33)	43 (12)	64 (19)	54 (18)
0.075	Abdomen	20	Multiple	120 (60)	53 (23)	86 (40)	53 (12)
0.1	Abdomen	42	Multiple	144 (57)	58 (20)	98 (38)	61 (18)
0.05	Abdomen	31	Single	53 (23)	-	41 (18)	69 (22)
	Buttock	31	Single	67 (45)	-	45 (21)	66 (23)
	Hip*	31	Single	69 (30)	-	48 (17)	62 (18)

* C_{max} and C_{avg} statistically different from abdomen

Steady state estradiol serum concentrations were measured in two well-controlled clinical trials in the treatment of menopausal symptoms of 3 month duration (Studies 1 and 2), and one trial in the prevention of postmenopausal osteoporosis of 2 year duration (Study 3). Table 2 provides a summary of these data.

Table 2

Mean (SD) steady-state estradiol serum concentrations (pg/ml) in clinical trials of 3 month (Studies 1 and 2) and 2 year (Study 3) duration

Alora (mg/day)	Study 1	Study 2	Study 3
0.025	-	-	24.5 (12.4)
0.05	46.9 (38.5)	38.8 (38.0)	42.6 (23.7)
0.075	-	-	56.7 (36.8)
0.1	99.2 (77.0)	97.0 (87.5)	-

In a 2-year, randomized, double-blind, placebo-controlled, prevention of postmenopausal osteoporosis study in 355 hysterectomized women, the average baseline-adjusted steady-state estradiol serum concentrations were 18.6 pg/ml (45 patients) for the 0.025 mg/day dose, 35.9 pg/ml (47 patients) for the 0.05 mg/day dose and 50.1 pg/ml (46 patients) for the 0.075 mg/day dose. These values were linearly related and dose proportional.

Distribution

No specific investigation of the tissue distribution of estradiol absorbed from **Alora** in humans has been conducted. The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In

postmenopausal women a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion
Estradiol, estrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates. The apparent mean (SD) serum half-life of estradiol determined from biopharmaceutic studies conducted with Alora is 1.75 ± 2.87 hours.

Special Populations
Alora has been studied only in healthy postmenopausal women (approximately 90% Caucasian). There are no long term studies in postmenopausal women with an intact uterus. No pharmacokinetic studies were conducted in other special populations, including patients with renal or hepatic impairment.

Drug Interactions
In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, phenytoin, carbamazepine, rifampin and dexamethasone may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as cimetidine, erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Adhesion
The adhesion potential of **Alora** was evaluated in a randomized clinical trial involving 408 healthy postmenopausal women who wore placebo systems corresponding to the 18 cm^2 size **Alora**. The placebos were applied twice weekly for 4 weeks on the lower quadrant of the abdomen. It should be noted that the lower abdomen, the upper quadrant of the buttocks or outer aspect of the hip are the approved sites of application for **Alora**. Subjects were instructed not to do strenuous activities, take baths, use hot tubs or swim. In 968 observations, there was a partial or complete adhesion rate of approximately 97%. The total detachment rate was approximately 3%. Adhesion potentials of the 9 cm^2, 27 cm^2 and 36 cm^2 sizes of **Alora** have not been studied.

CLINICAL STUDIES

Effects on vasomotor symptoms
Efficacy of **Alora** has been studied in a double blind/double dummy, randomized, parallel group, placebo-controlled trial involving a total of 268 postmenopausal women over a 12-week dosing period. Only women having estradiol and FSH serum concentrations in the postmenopausal range and who exhibited a weekly average of at least 60 moderate-to-severe hot flushes during the screening period were enrolled in the studies.

Patients received **Alora** 0.05 mg/day and a placebo system or **Alora** 0.1 mg/day and a placebo system, or two placebo systems dosed twice weekly over a 12-week duration. Measures of efficacy included mean reduction in weekly number of moderate-to-severe vasomotor symptoms when compared to the mean baseline average determined during a 2-week pre-dosing screening period. **Alora** was shown to be statistically better than placebo at Weeks 4 and 12 for relief of both the frequency (see Table 3) and severity of vasomotor symptoms.

Table 3

Mean Change from Baseline in Frequency of Moderate-to-Severe Vasomotor Symptoms for **Alora** Compared to Placebo (ITT)

Week of Therapy	Mean Change from Baseline		
	Alora 0.05 mg/day N = 87 Baseline = 90	**Alora** 0.1 mg/day N = 91 Baseline = 85	Placebo N = 90 Baseline = 92
4 *	- 57	- 70	- 45
8	- 65	- 77	- 49
12 *	- 68	- 79	- 54

*Indicates statistically significant differences between both strengths of Alora and placebo using an ANCOVA model adjusting for baseline.

Effects on vulvar and vaginal atrophy

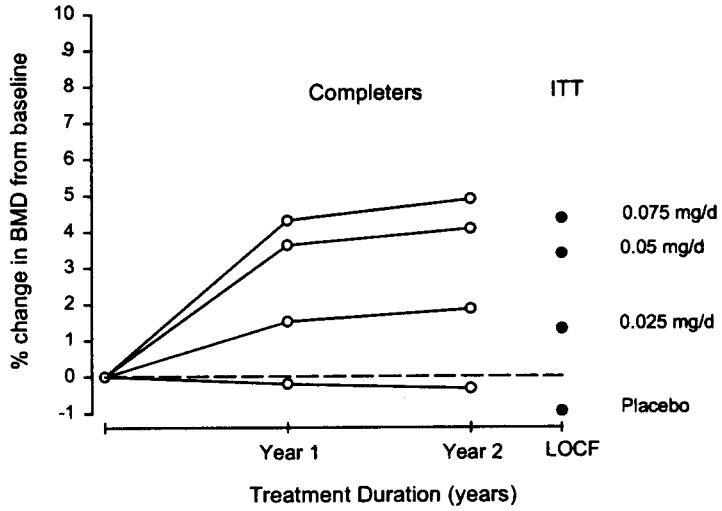
Vaginal cytology was obtained pre-dosing and at last visit in 54 women treated with **Alora** 0.05 mg/day, in 45 women treated with **Alora** 0.1 mg/day and in 46 women in the placebo group. Superficial cells increased by a mean of 18.7%, 23.7% and 8.7% for the **Alora** 0.05 mg/day, **Alora** 0.1 mg/day, and placebo groups, respectively. Corresponding reductions in basal/parabasal and intermediate cells were also observed.

Effects on bone mineral density

Lumbar spine bone mineral density (BMD) was measured by DEXA in a two-year, randomized, multi-center, double-blind, placebo-controlled, study in 355 hysterectomized, non-osteoporotic women (i.e., T-scores > -2.5). Eighty-six percent of the women were Caucasian, the mean age was 53.2 years (range 26 to 69), and the average number of years since menopause (natural or surgical) was not determined. Three Alora doses (0.025, 0.05 and 0.075 mg/day) were compared to placebo in terms of the % change in BMD from baseline to Year 2. The systems were applied every 3 or 4 days on alternate sides of the lower abdomen. All patients received 1000 mg of oral elemental calcium daily. The average baseline lumbar spine T-score was -0.64 (range -2.7 to 3.8). The % changes in BMD from baseline are illustrated in Figure 3.

Figure 3

Mean % change in BMD from baseline at 1 and 2 years after initiation of therapy with Placebo and Alora 0.025, 0.05 and 0.075 mg/day in the completer and intent-to-treat population with last observation carried forward (LOCF)



A total of 196 patients (44 – 0.025 mg/d, 49 – 0.050 mg/d, 45 – 0.075 mg/d, and 58 – placebo) were included in the completer population compared with 258 patients (59 – 0.025 mg/d, 64 – 0.050 mg/d, 63 – 0.075 mg/d, and 72 – placebo) in the intent-to-treat, last observation carried forward population.

All **Alora** doses were statistically superior to placebo for the primary endpoint, percent change in BMD from baseline. The mean 2-year (LOCF) percent changes in BMD for 0.025 mg/d, 0.05 mg/d, 0.075 mg/d, and placebo were 1.45%, 3.39%, 4.24%, and –0.80% respectively.

INDICATIONS AND USAGE

Alora is indicated in:

1. Treatment of moderate-to-severe vasomotor symptoms associated with the menopause.
2. Treatment of vulvar and vaginal atrophy.
3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
4. Prevention of postmenopausal osteoporosis. Estrogen replacement therapy reduces bone resorption and retards postmenopausal bone loss. When estrogen therapy is discontinued, bone mass declines at a rate comparable to that of the immediate postmenopausal period.

   The mainstays of prevention of postmenopausal osteoporosis are weight-bearing exercise, adequate calcium and vitamin D intake and, when indicated, estrogen. Postmenopausal women absorb dietary calcium less efficiently than premenopausal women and require an average of 1500 mg/day of elemental calcium to remain in neutral calcium balance. The average calcium intake in the US is 400-600 mg/day. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation of 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.

Risk factors for postmenopausal osteoporosis include early menopause, moderately low bone mass, thin body build, Caucasian or Asian race, family history of osteoporosis, and lifestyle (sedentary exercise habits, cigarette smoking and alcohol abuse).

CONTRAINDICATIONS

Estrogens should not be used in individuals with any of the following conditions:

1. Known or suspected pregnancy; see **PRECAUTIONS.** Estrogens may cause fetal harm when administered to a pregnant woman.
2. Undiagnosed abnormal genital bleeding;
3. Known or suspected cancer of the breast;
4. Known or suspected estrogen-dependent neoplasia;
5. Active deep vein thrombosis/pulmonary embolism or a history of these conditions.
6. Known hypersensitivity to any of the components of **Alora**.

WARNINGS

1. **Induction of Malignant Neoplasms.**
   a. ***Endometrial cancer***. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15 to 24-fold for five to ten years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

   b. ***Breast cancer***. While some epidemiologic studies suggest a very modest increase in breast cancer risk for estrogen-alone users versus non-users, other studies have not shown any increased risk. The addition of progestin to estrogen may increase the risk for breast cancer over that noted in non-hormone users more significantly (by about 24 to 40%), although this is based solely on epidemiologic studies, and definitive conclusions await prospective, controlled clinical trials.

   Women without a uterus who require hormone replacement should receive estrogen-alone therapy, and should not be exposed unnecessarily to progestins. Women with a uterus who are candidates for short-term combination estrogen/progestin therapy (for relief of vasomotor symptoms) are not felt to be at a substantially increased risk for breast cancer. Women with a uterus who are candidates for long-term use of estrogen/progestin therapy should be advised of potential benefits and risks (including the potential for an increased risk of breast cancer).

   All women should receive yearly breast exams by a health-care provider and perform monthly breast-self examinations. In addition, mammography examinations should be scheduled as suggested by providers based on patient age and risk factors.

2. **Thromboembolic Disorders**
   The physician should be aware of the possibility of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism, and pulmonary embolism) during estrogen replacement therapy and be alert to their earliest manifestations. Should any of these occur or be suspected, estrogen replacement therapy should be discontinued immediately. Patients who have risk factors for thrombotic disorders should be kept under careful observation.

   Venous thromboembolism. Several epidemiologic studies have found an increased risk of venous thromboembolism (VTE) in users of estrogen replacement therapy (ERT) who did not have predisposing conditions for VTE, such as past history of cardiovascular disease or a recent history of pregnancy,

surgery, trauma, or serious illness. The increased risk was found only in current ERT users; it did not persist in former users. The risk appeared to be higher in the first year of use and decreased thereafter. The findings were similar for ERT alone or with added progestin and pertain to commonly used oral and transdermal doses, with a possible dose-dependent effect on risk. The studies found the VTE risk to be about one case per 10,000 women per year among women not using ERT and without predisposing conditions. The risk in current ERT users was increased to 2 to 3 cases per 10,000 women per year.

Cerebrovascular disease. Embolic cerebrovascular events have been reported in postmenopausal women receiving estrogens.

Cardiovascular disease. Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

3. **Gallbladder Disease.** A 2 to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

4. **Hypercalcemia**. Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures should be taken to reduce the serum calcium level.

PRECAUTIONS

A. General

1. ***Addition of a progestin when a woman has not had a hysterectomy.*** Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

   There are, however, possible risks that may be associated with the use of progestins in estrogen replacement regimens. These include adverse effects on lipoprotein metabolism (e.g., lowering HDL and raising LDL) and impairment of glucose tolerance. The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects.

2. ***Cardiovascular risk***. The effects of estrogen replacement on the risk of cardiovascular disease have not been adequately studied. However, data from the Heart and Estrogen/Progestin Replacement Study (HERS), a controlled clinical trial of secondary prevention of 2,763 post-menopausal women with documented heart disease, demonstrated no benefit. During an average follow-up of 4.1 years, treatment with oral conjugated estrogen plus medroxyprogesterone acetate did not reduce the overall rate of coronary heart disease (CHD) events in postmenopausal women with established coronary disease. There were more CHD events in the hormone treated group than in the placebo group in year 1, but fewer events in years 3 through 5.

3. ***Elevated blood pressure.*** In a small number of case reports, substantial increases in blood pressure during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen.

4. ***Familial hyperlipoproteinemia.*** In patients with familial defects of lipoprotein metabolism, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications

5. ***Impaired liver function***. Estrogens may be poorly metabolized in patients with impaired liver function.

6. ***Hypothyroidism***. Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

7. ***Fluid retention***. Because estrogens may cause some degree of fluid retention, conditions which might be influenced by this factor, such as asthma, epilepsy, migraine and cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

8. ***Exacerbation of endometriosis***. Endometriosis may be exacerbated with administration of estrogen therapy.

9. ***Hypocalcemia***. Estrogens should be used with caution in individuals with severe hypocalcemia.

B. Patient Information

See text of Patient Information after the **HOW SUPPLIED** section.

C. Laboratory Tests

Estrogen administration should be guided by clinical response at the lowest dose for the treatment of vasomotor symptoms and vulvar and vaginal atrophy. Laboratory parameters may be useful in guiding dosage for the treatment of hypoestrogenism due to hypogonadism, castration and primary ovarian failure.

D. Drug/Laboratory Test Interactions

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered.

3. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.

5. Impaired glucose tolerance.

6. Reduced response to the metapyrone test.

7. Reduced serum folate concentration.

E. Carcinogenesis, Mutagenesis, Impairment Of Fertility
Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. (See **CONTRAINDICATIONS**)

F. Pregnancy Category X
Alora should not be used during pregnancy. See **CONTRAINDICATIONS.**

G. Nursing Mothers
The administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Estrogens are not indicated for the prevention of postpartum breast engorgement.

H. Pediatric Use.
Estrogen replacement therapy has been used for the induction of puberty in adolescents with some forms of pubertal delay. Safety and effectiveness in pediatric patients have not otherwise been established.

Large and repeated doses of estrogen over an extended time period have been shown to accelerate epiphyseal closure, which could result in short adult stature if treatment is initiated before the completion of physiologic puberty in normally developing children. If estrogen is administered to patients whose bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended during estrogen administration.

Estrogen treatment of prepubertal girls also induces premature breast development and vaginal cornification, and may induce gynecomastia. See **INDICATIONS** and **DOSAGE AND ADMINISTRATION** sections.

I. Geriatric Use
Clinical studies of **Alora** did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS
Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

See **WARNINGS** regarding induction of malignant neoplasms, thromboembolic disorders, gallbladder disease, and hypercalcemia. See **PRECAUTIONS** regarding cardiovascular risk and elevated blood pressure.

Incidence of adverse events > 2% of each treatment group is given in Table 4.

Table 4

Incidence of Adverse Events > 2% for Alora and Placebo Systems
(data are expressed as N and (%) of treatment group)

Body System Preferred Term	Placebo[a] (N=87)	Alora[a] 0.025 mg/day (N=89)	Alora[a] 0.05 mg/day (N=90)	Alora[a] 0.075 mg/day (N=89)	Alora[b] 0.1 mg/day (N=174)
Body As A Whole					
Accidental Injury	4 (4.6)	6 (6.7)	8 (8.9)	4 (4.5)	9 (5.2)
Allergic Reaction	2 (2.3)	4 (4.5)	4 (4.4)	2 (2.2)	1 (0.6)
Asthenia	4 (4.6)	7 (7.9)	4 (4.4)	0 (0)	4 (2.3)
Cyst	3 (3.4)	0 (0)	6 (6.7)	3 (3.4)	0 (0)
Flu Syndrome	9 (10.3)	8 (9)	12 (13.3)	9 (10.1)	6 (3.4)
Headache	11 (12.6)	10 (11.2)	8 (8.9)	5 (5.6)	37 (21.3)
Infection	2 (2.3)	2 (2.2)	3 (3.3)	3 (3.4)	2 (1.1)
Infection Fungal	1 (1.1)	3 (3.4)	9 (10)	4 (4.5)	0 (0)
Pain	11 (12.6)	9 (10.1)	5 (5.6)	6 (6.7)	16 (9.2)
Pain Abdominal	4 (4.6)	7 (7.9)	5 (5.6)	1 (1.1)	5 (2.9)
Pain Back	5 (5.7)	5 (5.6)	3 (3.3)	7 (7.9)	11 (6.3)
Pain Chest	4 (4.6)	4 (4.5)	2 (2.2)	1 (1.1)	2 (1.1)
Cardiovascular					
Hypertension	3 (3.4)	3 (3.4)	3 (3.3)	6 (6.7)	0 (0)
Migraine	2 (2.3)	6 (6.7)	2 (2.2)	0 (0)	2 (1.1)
Vasodilation	13 (14.9)	6 (6.7)	2 (2.2)	1 (1.1)	0 (0)
Digestive					
Constipation	4 (4.6)	3 (3.4)	6 (6.7)	1 (1.1)	3 (1.7)
Diarrhea	2 (2.3)	1 (1.1)	3 (3.3)	2 (2.2)	5 (2.9)
Dyspepsia	1 (1.1)	8 (9)	4 (4.4)	3 (3.4)	2 (1.1)
Flatulence	5 (5.7)	1 (1.1)	2 (2.2)	3 (3.4)	8 (4.6)
Gastroenteritis	2 (2.3)	3 (3.4)	4 (4.4)	3 (3.4)	0 (0)
Nausea	3 (3.4)	6 (6.7)	5 (5.6)	3 (3.4)	7 (4)
Metabolic And Nutritional					
Edema Peripheral	4 (4.6)	3 (3.4)	4 (4.4)	3 (3.4)	3 (1.7)
Weight Increased	4 (4.6)	3 (3.4)	2 (2.2)	4 (4.5)	1 (0.6)
Musculoskeletal					
Arthralgia	12 (13.8)	5 (5.6)	10 (11.1)	11 (12.4)	2 (1.1)
Bone Fracture Spontaneous	7 (8)	1 (1.1)	3 (3.3)	0 (0)	0 (0)
Joint Disorder	2 (2.3)	4 (4.5)	4 (4.4)	1 (1.1)	0 (0)
Myalgia	4 (4.6)	3 (3.4)	2 (2.2)	5 (5.6)	3 (1.7)
Nervous					
Anxiety	3 (3.4)	0 (0)	9 (10)	2 (2.2)	3 (1.7)
Depression	8 (9.2)	1 (1.1)	3 (3.3)	1 (1.1)	6 (3.4)
Dizziness	0 (0)	1 (1.1)	7 (7.8)	4 (4.5)	1 (0.6)
Hypesthesia	2 (2.3)	3 (3.4)	3 (3.3)	0 (0)	0 (0)
Insomnia	7 (8)	4 (4.5)	2 (2.2)	1 (1.1)	8 (4.6)

Body System Preferred Term	Placebo[a] (N=87)	Alora[a] 0.025 mg/day (N=89)	Alora[a] 0.05 mg/day (N=90)	Alora[a] 0.075 mg/day (N=89)	Alora[b] 0.1 mg/day (N=174)
Respiratory					
Asthma	1 (1.1)	3 (3.4)	3 (3.3)	1 (1.1)	2 (1.1)
Bronchitis	6 (6.9)	7 (7.9)	4 (4.4)	4 (4.5)	6 (3.4)
Cough Increased	2 (2.3)	1 (1.1)	4 (4.4)	1 (1.1)	6 (3.4)
Infection Respiratory	23 (26.4)	22 (24.7)	22 (24.4)	19 (21.3)	28 (16.1)
Pharyngitis	1 (1.1)	4 (4.5)	2 (2.2)	2 (2.2)	4 (2.3)
Pneumonia	4 (4.6)	4 (4.5)	4 (4.4)	1 (1.1)	1 (0.6)
Sinusitis	16 (18.4)	9 (10.1)	11 (12.2)	6 (6.7)	13 (7.5)
Skin					
Application Site Reaction	51 (58.6)	47 (52.8)	51 (56.7)	49 (55.1)	10 (5.7)
Hirsutism	0 (0)	2 (2.2)	2 (2.2)	4 (4.5)	1 (0.6)
Pruritus	4 (4.6)	2 (2.2)	1 (1.1)	6 (6.7)	9 (5.2)
Rash	5 (5.7)	6 (6.7)	8 (8.9)	4 (4.5)	5 (2.9)
Special Senses					
Conjunctivitis	2 (2.3)	2 (2.2)	3 (3.3)	2 (2.2)	0 (0)
Otitis Media	2 (2.3)	3 (3.4)	2 (2.2)	1 (1.1)	0 (0)
Urogenital					
Breast Enlargement	3 (3.4)	1 (1.1)	2 (2.2)	6 (6.7)	4 (2.3)
Infection Urinary Tract	2 (2.3)	5 (5.6)	4 (4.4)	2 (2.2)	3 (1.7)
Leukorrhea	1 (1.1)	3 (3.4)	2 (2.2)	4 (4.5)	3 (1.7)
Neoplasm Breast	6 (6.9)	3 (3.4)	5 (5.6)	1 (1.1)	3 (1.7)
Pain Breast	7 (8)	13 (14.6)	16 (17.8)	31 (34.8)	12 (6.9)
Vaginitis	6 (6.9)	0 (0)	3 (3.3)	0 (0)	14 (8)
Vaginal Bleeding[c]	4 (12.9)	NA	6 (8.7)	NA	29 (33.3)

a – Adverse events for the three lower Alora doses and placebo were obtained from the two year prevention of osteoporosis study

b – Adverse events for the highest Alora dose were obtained from two 12-week studies of the treatment of menopausal symptoms

c – Data reported for women with partially or fully intact uteri in the menopausal symptom study only (N=31 for Placebo; N=69 for Alora 0.05 mg/day and N=87 for Alora 0.1 mg/day)

NA – data not available

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen containing oral contraceptives by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

Alora should be administered twice weekly, as instructed. The adhesive side of the **Alora** system should be placed on a clean, dry area of skin. The recommended application site is the lower abdomen. In addition, the upper quadrant of the buttocks or outer aspect of the hip may be used. **Alora *should not be applied to the breasts.*** The sites of application should be rotated, with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may rub the system off. The system should be applied immediately after opening the pouch and removing the protective liner. The system should be pressed firmly in place with the palm of the hand for about 10 seconds, making sure there is good contact, especially around the edges.

In the event that a system should fall off, the same system may be reapplied. If necessary, a new system may be applied to another site. The original treatment schedule should be maintained.

Initiation of Therapy
For treatment of moderate-to-severe vasomotor symptoms, vulvar and vaginal atrophy associated with the menopause, hypogonadism, castration, or primary ovarian failure, treatment is usually initiated with **Alora** 0.05 mg/day applied to the skin twice weekly. The lowest dose and regimen that will control symptoms should be chosen and medication should be discontinued as promptly as possible. Attempts to discontinue or taper medication should be made at 3-month to 6-month intervals.

For the prevention of postmenopausal osteoporosis, the minimum dose of Alora that has been studied and shown to be effective is 0.025 mg/day applied to the skin twice weekly. Bone mineral density measurements should be repeated to monitor treatment efficacy. The dosage may be increased as necessary, depending on bone mineral density and adverse events.

In women who are not currently taking oral estrogens or in women switching from topical therapy or another transdermal estradiol therapy, treatment with **Alora** can be initiated at once. In women who are currently taking oral estrogens, treatment with **Alora** should be initiated one week after withdrawal of oral therapy or sooner if menopausal symptoms reappear in less than one week.

Therapeutic Regimen
Alora may be administered in a continuous regimen in patients who do not possess an intact uterus. In those patients with an intact uterus who are not using concomitant progestin therapy, **Alora** can be administered on a cyclic schedule (e.g. Three weeks of therapy followed by one week without) for the treatment of postmenopausal symptoms. However, no studies have been conducted using this intermittent regimen for the prevention of postmenopausal osteoporosis.

HOW SUPPLIED

Alora 0.025 mg/day (estradiol transdermal system). Each 9 cm^2 system contains 0.75 mg of estradiol USP for nominal delivery of 0.025 mg of estradiol per day when dosed in a twice weekly regimen.
NDC 52544-884-08 Patient Calendar Box of 8 Systems
NDC 52544-884-23 Patient Calendar Box of 24 Systems

Alora 0.05 mg/day (estradiol transdermal system). Each 18 cm^2 system contains 1.5 mg of estradiol USP for nominal delivery of 0.05 mg of estradiol per day when dosed in a twice weekly regimen.
NDC 52544-471-08 Patient Calendar Box of 8 Systems
NDC 52544-471-23 Patient Calendar Box of 24 Systems

Alora 0.075 mg/day (estradiol transdermal system). Each 27 cm^2 system contains 2.3 mg of estradiol USP for nominal delivery of 0.075 mg of estradiol per day when dosed in a twice weekly regimen.
NDC 52544-472-08 Patient Calendar Box of 8 Systems

Alora 0.1 mg/day (estradiol transdermal system). Each 36 cm^2 system contains 3.0 mg of estradiol USP for nominal delivery of 0.1 mg of estradiol per day when dosed in a twice weekly regimen.
NDC 52544-473-08 Patient Calendar Box of 8 Systems

Store at 15° - 30°C (59° - 86°F).
Do not store unpouched. Apply immediately upon removal from the protective pouch.
Discard used **Alora** in household trash in a manner that prevents accidental application or ingestion by children, pets, or others.

Distributed by: Watson Pharma, Inc.
a subsidiary of Watson Laboratories, Inc.
Corona, CA 92880

REVISED MONTH/YEAR

Estradiol Matrix
Transdermal Delivery System
NDA 21-310

Patient Package Insert

APPEARS THIS WAY
ON ORIGINAL

Watson Laboratories Inc.
Research Park
417 Wakara Way
Salt Lake City, UT 84108 USA

Patient Information

This leaflet describes the risks and benefits of treatment with Alora® (ah-LORE-ah). Read this information before treatment. Read the information you get each time you get medicine because there may be new information. Talk with your healthcare provider if you have any questions about this medicine.

What Is the Most Important Information I Should Know About Alora?

ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS
If you use any estrogen-containing medicine, it is important to visit your healthcare provider regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your healthcare provider should check any unusual vaginal bleeding to find out the cause. Women who do not have a uterus have almost no risk of endometrial cancer.

What is Alora?
Alora is a patch that contains the estrogen hormone estradiol. When applied to the skin as directed below, the Alora patch releases estrogen through the skin into the abdomen.

Alora Is Used In The Following Ways:

- **To reduce moderate or severe menopausal symptoms.**
  Estrogens are hormones made by a woman's ovaries. Between ages 45 and 55, the ovaries normally stop making estrogens. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause."

  When estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes" or "hot flushes"). In some women the symptoms are mild and in others they can be severe. Using estrogen drugs can help the body adjust to lower estrogen levels and reduce these symptoms. Most women have only mild menopausal symptoms or none at all, and do not need estrogen therapy for these symptoms. Other women may need to take estrogens for a few months while their bodies adjust to lower estrogen levels. Most women do not need estrogen replacement therapy for longer than six months for these symptoms.

- **To treat itching, burning, and dryness in and around the vagina due to menopause.**

- **To treat certain conditions in which a young woman's ovaries do not produce enough estrogen naturally.**

- **To help reduce your chances of getting osteoporosis (thin weak bones).**
  Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. Women who have menopause at an early age, are thin, smoke or have a family history of osteoporosis are more likely to develop osteoporosis.

  Alora may be used as part of a program which includes weight-bearing exercise like walking and running and taking calcium and vitamin D supplements to reduce your chances of getting osteoporosis. Before you change your exercise habits or calcium or vitamin D intake, it is important to discuss these lifestyle changes with your healthcare provider to find out if they are safe for you. You and your healthcare provider have agreed that you should take Alora to reduce your chances of getting osteoporosis. You may need to take Alora for a long period of time. Before you make any change in your use of Alora, talk with your healthcare provider.

Who Should Not Use Alora.

Do not use Alora if you

- **think you may be pregnant.** Using Alora while you are pregnant may harm your unborn child. Do not use Alora to prevent miscarriage.

- **have unusual vaginal bleeding.** If you develop vaginal bleeding while using Alora talk with your healthcare provider about proper treatment.

- **have or have had certain cancers.** Estrogens may increase the risk of certain types of cancer, including cancer of the breast or uterus. If you have or have had cancer, talk to your healthcare provider about the use of Alora.

- **have circulation problems.** Talk with your healthcare provider about your condition. Do not use Alora if you have blood clots or have had them in the past.

- **have recently had a baby.** Do not use Alora to stop your breasts from filling with milk after a baby is born.

- **are allergic to Alora or any of the ingredients in it.**

What Are the Possible Risks and Side Effects of Alora?

Common side effects include:

- Headache.
- Nausea and vomiting.
- Breast tenderness or enlargement.
- Retention of excess fluid. This may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease, or kidney disease.
- Vaginal spotting or bleeding.

Less common but serious effects include:

- Cancer of the uterus.
- Cancer of the breast.
- Gallbladder disease.
- Abnormal blood clotting.

These are some of the warning signs of serious effects:

- Unusual vaginal bleeding.
- Breast lumps.
- Pains in your legs.
- Severe headache and vomiting.
- Dizziness and faintness.
- Changes in vision or speech.

If you have any of these warning signs, or other unusual symptoms that concern you, call your healthcare provider right away.

What Can I Do to Lower My Chances of Getting a Serious Side Effect with Alora?

If you use **Alora**, you can reduce your risks by doing these things:

- **See your healthcare provider regularly.**

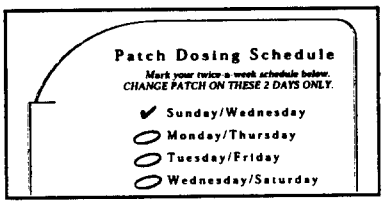
While you are using **Alora**, it is important to visit your healthcare provider at least once a year for a check-up. If you develop vaginal bleeding while taking **Alora**, you may need further evaluation. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast x-ray), you may need to have more frequent breast examinations.

How should I use Alora?

Before you begin, read all the information in these 5 steps.

Step 1. Choose your schedule for twice-a-week application.

Put on a new patch twice a week. Use one of the schedules on the inside flap of the patch box.



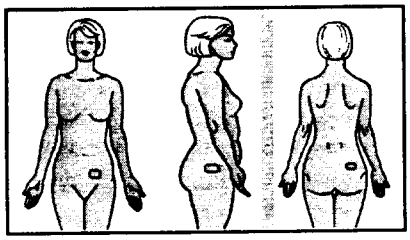
For example, if you apply your first patch on Sunday, take that patch off on Wednesday and put on a new one. Stay on this schedule as long as you use **Alora**. To help remind yourself, mark the schedule on the inside flap of the patch box. Put a check next to the first day you apply the patch. When you change your patch, don't put the new one in the same place. To help reduce the chance of skin redness or irritation, wait at least one week before you reuse a spot.

Step 2 Before you apply the patch

- Make sure the skin at the spot is:
- Freshly washed, but **dry and cool** (wait a few minutes after taking a hot bath or shower).
- Free of body powder or lotion.
- Free of cuts, rashes, or any other skin problem.

Step 3 Choose a spot for the patch

- **Place the patch on the lower abdomen (below the panty line) when you first start using Alora.**

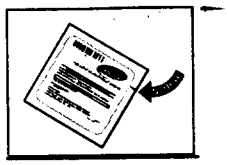
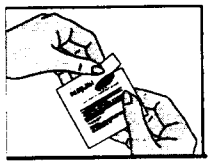


lower abdomen hips buttocks

- As you get used to applying **Alora**, you may want to try the hips or buttocks to see which area works best for you.
- Do not apply **Alora** to your breasts or any other parts of your body.

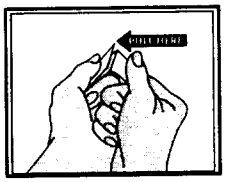
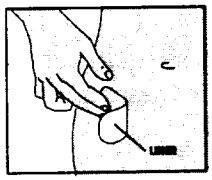
Step 4 How to apply the patch

- Open the pouch that contains the patch.

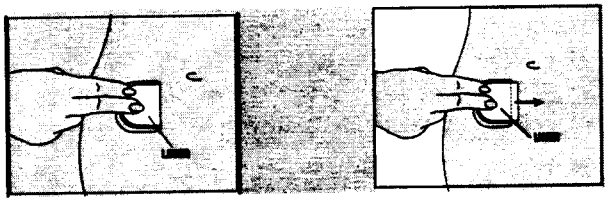
- Locate the notch on the top left or right corner of the pouch.
- Hold the pouch at the notch and tear off the top edge. Do not cut the pouch with scissors, which might damage the patch inside.
- Pull the patch out.

- **Apply one half of the patch to your skin.**

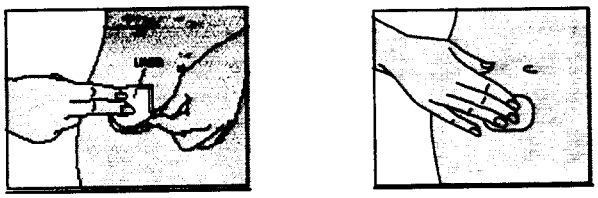



- Remove half of the liner, which covers the sticky surface of the patch. To find the liner, bend the patch in half. Then grab the clear straight edge of the liner and pull that piece off.
- Without touching the sticky surface, press the sticky half of the patch onto your skin. (If you touch the sticky surface, the patch may not stay on as well.)
- Rub the sticky half firmly to ensure full contact with your skin.

- **Apply the second half of the patch to your skin.**



- Bend the patch back over itself. Press down on the liner firmly.
- Push the liner forward a little to loosen the edge.



- Grab the loose edge at either corner and peel off the second piece of the liner. Try not to touch the sticky surface of the patch.

- **Press the entire patch firmly onto the skin with your finger tips.**

Press for at least 10 seconds to make sure the patch will stay in place. Be sure all of it sticks to your skin, even around the edges.

To help the patch stay in place:

- Try not to disturb the patch while putting on and removing clothes. It may help to place the patch where your underwear will cover it at all times.
- Be careful while changing clothes, washing or drying off, so that you do not catch the patch with your clothes or the towel.
- Try different sites on the lower abdomen, hips, or buttocks area to see what works well with your body and your clothing.
- If the patch starts to lift, simply press it back in place.

Step 5 Removing the patch

- **Take off the old patch.**
- **Fold it in half (sticky sides together) and throw it away out of the reach of children and pets.**

The skin under the old patch may look pink, but the color should fade away soon. In some cases, the skin may itch or look red; this may last from a couple of hours to a couple of days. Most of the time this is minor, and goes away by itself. But if it bothers you a lot or lasts longer than a few days, call your healthcare provider.

For Best Results, Stay with Your Patch Program

- **Replace your patch twice each week, on the two days you have chosen.** Until it becomes a habit, try:
  - Marking your schedule on the inside flap of the patch box;
  - Marking the days on your calendar;

SU	M	TU	W	TH	F	SA
Alora			Alora			

  - Linking the days you change your patch to other things that always happen on those days (e.g., an exercise class, meetings, etc.)

- **Handle each patch with care.**
  - Make sure the skin is clean, dry, and free of lotion and powder.
  - Try to avoid touching the sticky surface when applying the patch.
  - Be careful while changing clothes, washing or drying off, so that you do not catch the patch with your clothes or the towel.
  - If the patch starts to lift, simply press it back in place.

- **Keep working with your healthcare provider, pharmacist, or other health care professional.** Ask questions. If you have concerns, talk them over - don't just stop using the patch on your own. Remember, it may take a little time and some experience to get accustomed to using a patch.

- **Get your refills of the Alora patch before your supply runs out.**

How should I store Alora?

Store at 59° - 86°F (15° - 30°C). Do not store patches outside of their pouches. Apply the patch as soon as you take it out of the protective pouch.

General Information about Alora

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Your health care provider has prescribed this drug for you and you alone. Do not give the drug to anyone else. Do not use Alora for conditions for which it was not prescribed.

This leaflet provides a summary of the most important information about Alora. If you would like more information, talk with your healthcare provider. You can ask for information about Alora that is written for health professionals. You can also get more information by calling the toll free numbers 1-888-ALORA-4-U (1-888-256-7248).

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

/s/

David Orloff
4/5/02 01:11:46 PM

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-310

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #:	NDA 21-310	**Application Type:**	NDA
Sponsor:	Watson Laboratories	**Proprietary Name:**	Alora
Pharmaceutical Category:	Estrogen	**Route of Administration:**	Transdermal
Indication:	Prevention of Postmenopausal Osteoporosis	**Dosage:**	0.025 mg/day, 0.050 mg/day, 0.075 mg/day
Reviewer:	Patricia Beaston-Wimmer, M.D., Ph.D.	**Date Review Completed:**	October 10, 2001

Chemistry Reviewer: Elsbeth Chikhale, Ph.D.

Pharmacology Reviewer: Karen Davis-Bruno, Ph.D.

Biopharmaceutics Reviewer: Wei Qiu, Ph.D.

Statistical Reviewer: Todd Sahlroot, Ph.D.

REVIEW SUMMARY: See Executive Summary

OUTSTANDING ISSUES: none

RECOMMENDED REGULATORY ACTION: N drive location:

New clinical studies	_____	**Clinical Hold**	_____	**Study May Proceed**
NDA, Efficacy/Label supplement:	_____	**Approvable**	_____	**Not Approvable**
	X	**Approve**		

SIGNATURES: Medical Reviewer: Patricia Beaston-Wimmer, M.D., Ph.D.

Medical Team Leader: Eric Colman, M.D.

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Table of Contents

Executive Summary

I. Recommendations

Watson Laboratories has submitted the results of one clinical study to support the new indication, prevention of postmenopausal osteoporosis, for Alora (transdermal estradiol). The data support the indication for the currently approved doses 0.050, and 0.075 mg/day and a new dose, 0.025 mg/day. This reviewer recommends approval of the new indication for the above doses. Recommendations regarding labeling changes are found in the Appendix. There are no recommendations for Phase 4 Studies.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Alora, transdermal estrogen, has been approved for the treatment of postmenopausal symptoms related to estrogen deficiency. Watson seeks approval for a new indication, prevention of postmenopausal osteoporosis. This submission contains data from one 2-year clinical trial in which 355 patients were randomized to 3 doses of estrogen and placebo.

B. Efficacy

This study compared the effect of three doses (0.025, 0.050, 0.75 mg/day) of estrogen to placebo on the change in lumbar spine bone mineral density (LS BMD) over a 2-year period in postmenopausal women with a history of hysterectomy. The primary measure of efficacy was mean percent change in LS BMD from baseline to exit. There was a statistically significantly larger mean percent change for the 0.025, 0.05, and 0.75 doses of estrogen (1.65, 4.08, 4.82%, respectively) compared to placebo (-0.59 %). Although across study comparisons of efficacy cannot be made easily because of dissimilarities in patient populations enrolled, in general, the efficacy of Alora was similar to other approved estrogens.

C. Safety

Three-hundred and fifty-five (355) patients were randomized to the study. Safety analyses included all subjects who received at least one dose of stud drug. The mean duration of exposure was 495.6 days (median 722, range 4 to 785). The most common side effects included breast pain and hypertension — events consistent with estrogens as a class. Since the patients in this study all had a history of hysterectomy there are no data on the effects of Alora on the endometrium nor are there data regarding the use of Alora with a progestational agent. Application site reactions were reported in 55.8% of participants with similar frequency across groups. In comparison, the incidence of application site reactions reported for another transdermal estrogen (Vivelle) was 8.5%.

Safety labs and mammography were appropriately planned in the study. Although mammography provided useful screening and follow-up data for breast cancer, the relatively short duration and small sample size of the study do not lend themselves to an accurate assessment of breast cancer risk. There is no reason, however, to believe that an Alora associated risk for developing breast cancer would be different than that observed with other estrogens.

A potential drug-drug interaction was overlooked in this study. Current labeling for estrogens discuss the increase in thyroid binding globulin (TBG) observed in patients initiating estrogen therapy but states that 'free T_4 and free T_3 concentrations are unaltered. This is true only for those patients with an intact thyroid axis. Patients who are dependent on exogenous thyroid hormone cannot increase thyroid hormone production in response to increased TBG and are at risk of under treatment. There was no provision for monitoring patients on thyroid hormone treatment in this study. (Changes to the label have been suggested in the Appendix on labeling changes.)

D. Dosing

A 'no effect' dose has not been established. The lowest dose used in this study (25 mcg) gave similar efficacy relative to placebo as that seen with that same dose of Vivelle, another transdermal estrogen. While statistically significant, this low dose provided a relatively small improvement in BMD over the time studied (2 years). Because fracture data for estrogens are not required for approval and there are no long term data available for this lower dose, it would be difficult to argue that pursuing a lower dose would provide adequate efficacy.

The relationship of adverse events to dose of estrogen are well described. They include breast tenderness and increased risk of endometrial cancer, breast cancer and deep vein thrombosis with higher doses. While a lower dose (0.025mg/d) has demonstrated efficacy for the prevention of PMO, it may be less efficacious for the treatment of vasomotor instability, Those adverse events that are dependent on the hepatic 'first-pass effect' such as increased triglycerides appear to be attenuated by transdermal delivery.

[redacted]

E. Special Populations

Alora is indicated for use by postmenopausal women and therefore not indicated for use in males, children (a pediatric waiver was requested) or pregnant women.

The majority (86.5%) of the subjects in this study were white. Osteoporosis is generally a condition of thin, white or Asian women. There is insufficient clinical information available to make recommendations for other populations.

The safety and effectiveness in geriatric patients (over age 65) have not been established (current labeling). Estrogens are prescribed to many patients in this age group for prevention and treatment of osteoporosis. While some patients enrolled in this study were ≥ 65 years of age, the study was not designed to specifically address safety and efficacy in this population.

Clinical Review[*]

I. Introduction and Background

Postmenopausal osteoporosis (PMO) is a common disorder and has been well described. It is characterized by an accelerated bone turnover in the first six months after estrogen deprivation, natural or surgical. After the initial 6-months the rate of turnover slows and plateaus. An imbalance in destruction and production of bone results in decreased bone mass and loss of bone microarchitecture. The remaining bone demonstrates normal histology without evidence of osteomalacia. Hormone replacement therapy (HRT) has been shown to prevent the rapid increase in turnover and to preserve bone mineral density. In addition to HRT modification of risk factors for osteoporosis are recommended. These include weight bearing exercise, adequate intake of calcium and Vitamin D, cessation of tobacco use and moderate caffeine intake, and maintenance of a reasonable body weight.

A number of estrogen products, oral and transdermal, are in use for the prevention of PMO. In general no difference in efficacy has been demonstrated for this indication between the two approved routes of administration. The transdermal route avoids the 'first pass effect' of the liver resulting in less metabolism of estradiol to estrone. The clinical significance of increased estradiol delivery has not been established, but the hypertriglyceridemia observed in some patients taking oral estrogens is not seen with transdermal estradiol use. Because estrogen treatment is associated with increased risk of breast cancer, endometrial cancer and venous thrombosis, companies have attempted to identify the 'lowest effective dose'.

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Alora, 17ß-estradiol transdermal system, was approved by DRUDP in December 1996 (NDA 20-655) for the treatment of moderate to severe vasomotor symptoms associated with menopause, treatment of vulval and vaginal atrophy, and treatment of hypogonadism, castration, or primary ovarian failure. The currently approved doses are 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day. Watson is seeking a new indication of "prevention [redacted] of postmenopausal osteoporosis" for the currently approved doses and a new dose, 0.025 mg/day.

B. State of Armamentarium for Indication

Currently approved drugs for prevention and treatment of osteoporosis are limited to therapies that decrease bone resorption and include 1) other estrogen products and the selective estrogen receptor modifier (SERM) raloxifene, 2) bisphosphonates, and 3) calcitonin. Calcium and Vitamin D supplementation are recommended to postmenopausal women as part of good clinical practice. To date no therapies have been approved that promote bone formation.

[*] Direct quotes from the NDA submission are *italicized*, Reviewer's comments are **bolded**.

C. Important Milestones in Product Development

FDA Agreements

April 1, 1996 – The Divisions (DMEDP and DRUDP) concurred that inclusion of only hysterectomized women would be acceptable in the osteoporosis study. The labeling would reflect that the clinical study was performed solely on this patient population. Additionally, an osteoporosis claim could be obtained [redacted] if estrogen equivalence with their estradiol patch could be demonstrated.

June 27, 1996 – Statistical analysis plan for the Phase III study would include a last observation carried forward analysis.

July 31, 1996 – The Divisions agreed that measurement of trabecular bone density in lumbar bone rather than cortical bone density in the hip would be appropriated as long as the product labeling disclosed this as the primary study endpoint. Consistent with the current guideline for development of products for osteoporosis , the Divisions recommended a washout period of six months from prior estrogen treatment be incorporated into the study design because of the effects of prior estrogen treatment on bone marrow density. [redacted]

May 20, 1997 – DRUDP approved the Watson's request to shorten the washout period from previous estrogen therapy from 6 months to 2 months. (Additional changes in the inclusion and exclusion criteria are noted in the section describing the study population.)

The Divisions concurred that conclusions reached in the hysterectomized patient population could be extrapolated to non-hysterectomized women.

If the 0.025 mg/day dose was determined to be effective, the higher strengths of Alora [redacted] would still be approved for vasomotor symptoms but the product labeling would need to address the finding of a lower effective dose for postmenopausal osteoporosis.

Formulation Change

Watson changed [redacted] It appears from the records that the 'old' formulation was used for the lowest dose studied, 0.025 mg. There is no documentation regarding the formulation used of the other doses employed in the study. DRUDP approved the use of the new formulation for the 0.05, 0.075, and 0.100 mg/day doses. The biopharmaceutic review from DRUDP was reviewed. There was an approximately 95% bioequivalence between the new and old formulations using the 18 cm^2 system. Since the 9 cm^2 system uses the same formulation at half the size a similar bioequivalence would be expected.

[redacted]

Prior FDA reviews of Alora

1) NDA 20-6— Sponsor TheraTech, Inc., Division DRUDP, Review Date 11/14/96.
2) NDA 20-655/S-002, Sponsor TheraTech, Inc., Division DRUDP, Review Date 10/15/97Biopharmaceutic and adhesion comparison [redacted]

D. Other Relevant Information

Trade Secret [redacted]

The trial that is the subject of this review was started by Proctor and Gamble Pharmaceuticals and transferred to Watson Laboratories, Inc.

II. Clinically Relevant Findings From Chemistry, Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Per Chemistry reviews (initial and current NDAs). According to Chemistry, [redacted] changed from the time of the initial approval and completion of the study in this NDA. The formulation used with the individual patients in this study is not recorded in the data base provided. The new formulation has been evaluated by DRUDP and was approved. Additional information regarding the lower dose is found in the chemistry review for this NDA.

III. Human Pharmacokinetics (PK) and Pharmacodynamics (PD)

Per PK/PD reviews (initial and current NDAs). According to Pharmacokinetics, information regarding the change [redacted] was submitted to DRUDP. The drug delivery based on drug depletion was within the acceptable range. Additional information regarding the lower dose are found in the PK/PD Review for this NDA.

IV. Description of Clinical Data and Sources

This submission consisted of 38 paper volumes and an electronic data set. The results of one clinical trial were provided. Alora has been marketed since December 1996. Forty-two (42) adverse events were recorded in the AERS system (as of 8/31/01) and were generally consistent

with estrogens as a class. .There is an extensive literature on estrogens and postmenopausal osteoporosis, including the data obtained in the more recently completed HERS study.

V. Clinical Review Methods

A. Evaluation of Material Submitted

All submitted information was reviewed. Both efficacy data and safety data were confirmed or recalculated using the electronic data set included with the submission. The quality and organization of the data set provided were poor. While the quality of the data set made the data confirmation process time consuming, it did not prevent review of the major components of the submission. Previous reviews and current labels for this and other approved estrogens were also reviewed.

B. Evaluation of Financial Disclosure

Watson has provided the names of 25 primary investigators and 147 sub-investigators. Disclosure of financial interests was provided [redacted]

VI. Review of Efficacy

A. General Approach to Review of the Efficacy

In order to demonstrate efficacy of an estrogen in the prevention of PMO, the Guidance for Evaluation of Drugs for Osteoporosis requires demonstration that drug-treated subjects have a mean increase in BMD that is statistically significantly greater than the change in placebo-treated subjects. (This is in contrast to non-estrogen drugs for which fracture prevention data are required.) Watson has demonstrated statistically significant efficacy in preserving or improving BMD in postmenopausal women for all estrogen doses tested when compared to placebo. However, based on the trial design, there are limitations to the claims that can be made in the label. These difference are noted on the annotated version of the label.(see Appendix)

B. Detailed Review of Trial

This submission consisted of a single study.

Clinical Study

Title: A randomized, parallel-group, double blind, double-dummy, placebo-controlled, multi-center, Phase III, dose-ranging study of 24 months (26 cycles of 28 days each) duration in postmenopausal women who have had a hysterectomy.

Objective: The objective was to establish the minimally effective estradiol dose that significantly prevents lumbar spine bone loss, as measure by bone mineral density (BMD), when compared to placebo.

Study Design:

Patient Population:

Inclusion Criteria

Female <70 years old at baseline visit (Protocol Amendment 1, Change 2);

Had a hysterectomy with or without bilateral oophorectomy and FSH value >40 mIU/ml plus serum estradiol <20 pg/ml as adequate documentation of menopausal status. Surgical menopause (documented bilateral oophorectomy) must be at least 12 months before starting study drug. [An estradiol level of 23 pg/ml or less (based on the assay precision of ——, without regard to the FSH level, was used as hormonal definition of menopause as documented in a Protocol Amendment].

Had documented normal TSH value at screening, if subject was taking thyroid replacement therapy;

Had a normal screening mammogram (documented results of a normal mammogram within 6 months was acceptable);

Agreed to take estrogen for the 2-year study duration;

Had a lumbar spine bone mineral density (BMD) by — >0.722 g/cm^2 on a —— scanner, or >0.882 g/cm^2 on the —— machine; **(These values correspond to a T-score ≥ -2.5.)**

Was ambulatory; and

Was able and willing to participate in the study as evidenced by providing written informed consent.

Exclusion Criteria

Had a history of intolerance to estrogen or related compounds, or had a known or suspected hypersensitivity to any constituents of transdermal systems;

Received oral estrogen therapy within the past 2 months including phytoestrogens (Protocol Amendment, Change 1);

Had evidence of clinically significant organic disease on history or physical examination that, in

the opinion of the Investigator and/or P&GP Protocol Physician, would prevent the subject from completing the study;

Had evidence of a clinically significant psychiatric disorder, e.g., major depression, etc., on history or physical examination which, in the opinion of the Investigator and/or P&GP Protocol Physician, would prevent the subject from completing the study;

Had a history of cancer with the exception of:
Basal cell carcinoma with a documented 6-month remission,
Carcinoma in situ of the uterus or cervix treated by hysterectomy;

Had a history of hyperparathyroidism, untreated hyperthyroidism, or osteomalacia within 1 year before starting study drug;

Had contraindications to estrogen use as determined by a history of:
Carcinoma of the breast,
Estrogen dependent neoplasia,
Thrombophlebitis,
Thromboembolic disorders;

Had abnormal laboratory parameters at screening including:
Hemoglobin A1c > 10% of the upper limit of normal,
*Fasting serum total cholesterol, LDL, and triglycerides > 25% above the upper limit of normal,
*Fasting serum HDL > 20% below the lower limit of normal,
(*removed lipid levels as exclusionary criteria, Amendment1, Change 4)
Serum creatinine > 2 mg/dl,
ALT or AST results > 1.5 times the upper limit of normal,
Bilirubin results > 2 times the upper limit of normal.

Had a history of using the following medications within 3 months of starting study drug or for more than 1 month within the last 6 months before study drug:
> 400 µg/day of inhaled beclomethasone or equivalent,
Oral or parenteral glucocorticoids (≥5 mg prednisone or equivalent/day),
Anabolic steroids,
Calcitonin,
Vitamin D supplements (>800 IU/day) orally,
Calcitriol;

Had a history of using any of the following medications within 3 months of starting study drug:
Any bisphosphonate,
Fluoride (>10 mg/day);

Participated in another clinical study involving active intervention within 30 days prior to start of dosing in this study;

Had abnormalities on the AP or lateral lumbar radiographs such as severe scoliosis (>15 to 20 degrees depending on the degree of associated osteophytosis), spinal fusion, aortic calcification, or severe fracture deformation that would preclude precise measurements as determined by the radiographic screening facility. At least 2 lumbar vertebrae (LI-L4) in the scanning field must be without fracture for analysis; or

Had physical characteristics (such as body and girth) which would preclude precise measurements as evidenced by review of the baseline by the Investigator.

Comment: The inclusion/exclusion criteria are generally reasonable and approximate the criteria in the guidance for the study of estrogen for the prevention of postmenopausal osteoporosis. The majority of the variations from the guidance were agreed on as noted. However, the inclusion/exclusion criteria allow for enrollment of patients who would not be considered to have risk factors for developing postmenopausal osteoporosis, this will be discussed further in the description of the study population. There is no record regarding the recruitment process for this study or by what criteria potential patients failed to meet the criteria of the study. Additionally, there was no description of the methods used to confirm that patients did not have 'untreated hyperthyroidism', hyperparathyroidism or abnormalities of Vitamin D regulation. It is important for prescribing physicians to have data demonstrating how study populations compare to the general population to make clinical judgements for treating individual patients.

Study Medications:

Four treatment groups. Double-Dummy approach:

Alora 0.025 mg/day (9cm^2 system) and placebo (18 cm^2 system)
Alora 0.050 mg/day (18cm^2 system) and placebo (9 cm^2 system)
Alora 0.075 mg/day (9cm^2 and 18 cm^2 systems)
Placebo (9cm^2 and 18 cm^2 systems)

Subjects were randomized to one of four treatment groups. A treatment regimen was defined as the application of 2 systems, one 9cm^2 and one 18 cm^2 to the same side of the abdomen every 3.5 days. The commercial Alora product is approved for twice weekly applications. The system application sites were alternated form the left to the right side of the abdomen every 3.5 days. A subject was instructed to allow 1 week between applications of systems to a particular site.

Comment: The doses used in this study represent the attempt to identify the lowest efficacious dose to limit adverse events related to estrogen exposure.

All patients received 1000 mg of oral elemental calcium in the form of 2 OsCal tablets daily.

Comment: It is recommended that postmenopausal women have a 1500 mg daily intake of elemental calcium and supplemental Vitamin D of 400-800 IU daily. The 1000 mg of oral calcium given to study patients is probably adequate; there was no Vitamin D given in this study. Review of the concomitant medications revealed that a number of patients used vitamin and herbal supplements. The data structure makes it difficult to determine the distribution of patients taking supplements (those containing calcium and/or Vitamin D) that might affect BMD. Vitamin D levels were not obtained at screening to rule out deficiency nor was Vitamin D supplemented during the study. Patients who might have been Vitamin D deficient prior to the study may have benefited (by increase in BMD) by taking Vitamin D or Vitamin D containing supplements after the study had started.

Efficacy Assessments

Primary efficacy parameter: *The mean percentage change from baseline in lumbar spine BMD at the end of 2 years.*

Secondary efficacy parameters: *The percent change from baseline in lumbar spine BMD at Cycle 13, and the actual change from baseline in lumbar spine BMD at Cycle 13 (1-year) and Cycle 26 (2-years).*

BMD measurements were obtained on either [redacted] machines. The [redacted] were evaluated at a central facility, [redacted] The machines provide different BMD measurements. In order to make the baseline readings from the machines comparable, raw BMD measurements were standardized using the following algorithm:

standardized BMD = 1.0755 x BMD [redacted]
= 0.9522 x BMD [redacted]

Comment: According to the protocol submitted, radiographs of the lumbar spine were to be performed at both the screening and Cycle 26 (or exit) visit to *ensure the integrity of the lumbar area being assessed by* [redacted] In the electronic data base only information on radiographs at exit are provided. Watson was contacted to obtain information regarding radiographs from screening. Waston stated that the information in the data base represented screening radiographs and that exit radiographs were not performed. This issue was clarified in attempts to correctly identify the intent to treat population and for information regarding vertebral fractures.

Although [redacted] were obtained at the end of the first year of treatment (Cycle 13), there did not appear to be safety escape criteria for excessive bone loss.

Statistical Analysis

An overall analysis of variance (ANOVA) method was used to compare the treatment groups with respect to the primary efficacy parameter. A total of approximately 336 subjects were to be recruited. Each treatment group was to be allocated approximately 84 subjects. Assuming a 50% drop out rate by the end of 2 years, 42 subjects per treatment group were expected to complete the study. This sample size provided 90% power to detect a 5% difference (standard deviation = 7%) between an active estrogen arm and placebo in the rate of bone loss based on 2-sample t-test at the 0.05 significance level. A full discussion of the statistical analysis can be found in the Biometrics review by Dr. Sahlroot.

Study Schedule

The following is a tabular summary of the trial procedures and schedule. Details regarding specific safety and efficacy parameters are discussed in the appropriate sections.

STUDY SCHEDULE	CYCLE												
Procedure	Screen	Baseline	1	2	3	5	7	10	13	16	20	23	26*
Informed Consent	✓												
Personal and Demographic Data	✓												
Medical and Drug History	✓												
Physical, Breast & Pelvis Exams	✓						✓		✓		✓		✓
Mammogram (or report if < 6 months)	✓								✓				✓
FSH and Estradiol	✓												
AP & Lateral Lumbar Radiograph	✓												
— - Lumbar spine	✓								✓				✓
Hematology	✓						✓		✓		✓		✓
Serum Chemistry	✓						✓		✓		✓		✓
Carbohydrate Metabolism	✓						✓		✓		✓		✓
Serum Lipid Profile (TC/HDL/LDL/TG)	✓						✓		✓		✓		✓
Coagulation Profile (PT, PTT)	✓						✓		✓		✓		
Serum Hormone Levels (E2, E1)		✓							✓		✓		
Concomitant Medications	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	
Vitals Signs	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	
EKG		✓											
Dispense Study Drug		✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	
Dispense Calcium		✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	
Study Medication Compliance Check			✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse Event Assessment			✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Telephone Contact				✓									
Lateral Lumbar Radiograph													✓

*All procedures listed at Cycle 26 should be carried out at the patient's exit visit if the patient discontinues at an earlier visit.

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Results

Population Demographics

The study population enrolled is described in the table below.

Parameter	Estradiol 0.025 mg/day (N=89)		Estradiol 0.050 mg/day (N=90)		Estradiol 0.075 mg/day (N=89)		Placebo (N=87)		Overall (N=355)	
Age (years)										
Mean ± SE	51.6 ± 0.9		53.7 ± 0.7		54.0 ± 0.7		53.8 ± 0.7		53.2 ± 0.4	
Median	52		53		54		54		54	
Range	29-69		30-69		36-69		26-68		26-69	
Weight (lbs)										
Mean ± SE	171.2 ± 4.0		165.9 ± 3.58		169.6 ± 3.79		161.8 ± 3.36		167.2 ± 1.9	
Median	164		162.5		165		160.5		162.5	
Range	94.5-281.0		100.0-255.0		103.0-307.0		100.1-262.8		94.5-307.0	
Height (ins)										
Mean ± SE	64.6 ± 0.3		64.1 ± 0.2		64.4 ± 0.3		64.4 ± 0.3		64.3 ± 0.1	
Median	64.5		64.2		64.5		64.5		64.5	
Range	57.0-70.0		59.5-69.0		59.0-70.0		59.5-68.8		57.0-70.0	
BMI (kg/m^2)*										
Mean ± SE	29.2 ± 0.7		28.5 ± 0.6		28.9 ± 0.6		27.5 ± 0.5		28.5 ± 0.3	
Median	27.9		28.2		27.6		27.1		27.6	
Range	15.2-48.5		16.9-43.3		18.0-48.7		17.2-41.3		15.2-48.7	
Yrs since hysterectomy			89							
Mean ± SE	15.7 ± 0.93		15.6 ± 0.76		16.9 ± 0.89		16.2 ± 0.92		16.1 ± 0.44	
Median	16.6		16.0		17.0		16.4		16.5	
Range	0.7-36.8		1.2-33.6		1.1-36.1		0.8-36.4		0.7-36.8	
L-Spine T-Score			89							
Mean ± SE	-0.69 ± 0.12		-0.47 ± 0.13		-0.72 ± 0.12		-0.68 ± 0.12		-0.64 ± 0.06	
Median	-0.80		-0.60		-0.80		-0.80		-0.75	
Range	-2.5-3.3		-2.7-3.2		-2.6-3.8		-2.5-3.6		-2.7-3.8	
	n	%	n	%	n	%	n	%	n	%
Race										
Caucasian	78	87.6	76	84.4	79	88.8	74	85.1	307	86.5
Black	6	6.7	7	7.8	6	6.7	6	6.9	25	7.0
Hispanic	3	3.4	4	4.4	1	1.1	5	5.7	13	3.7
Other	2	2.2	3	3.3	3	3.4	2	2.3	10	2.8
Tobacco Use										
Never Used	35	39.3	51	56.7	36	40.4	41	47.1	163	45.9
Previously Used	26	29.2	23	25.6	28	31.5	24	27.6	101	28.5
Currently Used	28	31.5	16	17.8	25	28.1	22	25.3	91	25.6
Alcohol Use										
Never Used	19	21.3	23	25.6	25	28.1	22	25.3	89	25.1
Previously Used	13	14.6	8	8.9	14	15.7	5	5.7	40	11.3
Currently Used	57	64.0	59	65.6	50	56.2	60	69.0	226	63.7
Estrogen Use										
Never Used	75	84.3	72	80.0	76	85.4	72	82.8	295	83.1
Previously Used	14	15.7	18	20.0	13	14.6	15	17.2	60	16.9

Statistics: Pairwise comparisons were made between each treatment group and placebo. There were no statistical differences between groups for the above parameters.
*BMI data generated by this reviewer using the data base provided.
All patients are from the USA.

The mean age at hysterectomy was 37.1 years (range 19-62). The mean time since hysterectomy was 16.1 years (range 0.7-36.8). At baseline, the mean estradiol level was 3.4 pg/ml (range 0-112), and mean FSH level was 66.3 IU/l (range 4-171). The mean lumbar spine BMD was 1.051

g/cm^2 (range 0.82-1.56). The mean lumbar spine T-score was –0.64 (range -2.7 to -3.8; 6 subjects had T-score ≤ -2.5, 3 completed the study). There were no statistical differences among the groups for these parameters.

Comment: The time since menopause is not known for the majority of the subjects. The information available in the data set is 'time from hysterectomy' (months and years) and history of oophorectomy (yes or no). One hundred and sixty-nine (169, 47.6%) had no history of oophorectomy. The menopausal status prior to surgery, hysterectomy and oophorectomy, was not reported. Therefore, although Watson provides a number of analyses using time from hysterectomy as a variable, these analyses offer little information because it is not the presence of the uterus but the estrogen status of the patient that influences bone mineral density.

The time from discontinuation of estrogen therapy was not found in the data set. There is accelerated bone loss in the first 6-months after discontinuation of estrogen therapy with a decrease in the rate of loss after that initial period. Failure to equally distribute patients with a 'short time from discontinuation of estrogen' could affect the comparisons among groups. However, the number of patients who received estrogen treatment prior to this trial was relatively small and should not effect the overall findings of the study. Similarly, there was a wide range in time since hysterectomy with the majority (87.6%) of the patients having had a hysterectomy > 5 years prior to enrollment in the study. Therefore the patient population enrolled in this study is more likely to have completed the rapid turnover phase of the early postmenopausal state and would give less information regarding prevention.

Mean BMI was 28.5 kg/m^2 (median 27.6, range 15.17 to 48.69) and was similar across groups. In general, obese women are not considered to be at risk for developing PMO because of higher circulating estrogens, principally estrone (which is formed by peripheral aromatization of androstenedione). With the exception of a tobacco use history, there was little evaluation of other osteoporosis risk factors in this study population making it difficult to determine if these overweight and obese patients would have been at risk for developing PMO.

Subject Disposition

A total of 355 patients were enrolled in the study. The following tables summarize the patient disposition by treatment and the reasons for premature termination.

Subject Disposition	Estradiol 0.025 mg/day		Estradiol 0.050 mg/day		Estradiol 0.075 mg/day		Placebo		Overall	
	n	%	n	%	n	%	n	%	n	%
Randomized	89	100.0	90	100.0	89	100.0	87	100.0	355	100.0
Completed	44	49.4	49	54.4	45	50.6	58	66.7	196	55.2
Premature Termination	45	50.6	41	45.6	44	49.4	29	33.3	159	44.8
≥ 1 follow-up BMD	60	67.4	64	71.1	63	70.8	72	82.8	259	73.0

Reason for Termination	Estradiol 0.025 mg/day (N=89)		Estradiol 0.050 mg/day (N=90)		Estradiol 0.075 mg/day (N=89)		Placebo (N=87)		Overall (N=355)	
	n	%	n	%	n	%	n	%	n	%
Total Premature Terminations	45	50.6	41	45.6	44	49.4	29	33.3	159	44.8
Adverse Event										
Total	14	15.7	12	13.3	20	22.5	6	6.9	52	14.6
Application-Site Reaction	7	7.9	8	8.9	9	10.1	0	0	24	6.8
Investigator Recommendation	1	1.1	2	2.2	0	0	0	0	3	0.8
Protocol Violations										
Total	4	4.5	7	7.8	1	1.1	3	3.4	15	4.2
Inclusion Criteria	0	0	1	1.1	0	0	0	0	1	0.3
Exclusion Criteria	0	0	3	3.3	0	0	1	1.1	4	1.1
Non-Compliance										
Dose Schedule	0	0	0	0	1	1.1	0	0	1	0.3
Visit Schedule	4	4.5	3	3.3	0	0	2	2.3	9	2.5
Excluded Concomitant Medication	1	1.1	0	0	1	1.1	0	0	2	0.6
Voluntary Withdrawal	15	16.9	13	14.4	11	12.4	12	13.8	51	14.4
Lost to Follow-up	8	9.0	7	7.8	11	12.4	8	9.2	34	9.6
Death	2	2.2	0	0	0	0	0	0	2	0.6

N= Number of subjects randomized to each treatment group
n= Number of subjects by reason for premature termination

Comment: Analysis of the data was confused by the reference to the 'Cycle 26' time point, the endpoint of the study. There were no 'Cycle 26' data in the data set provided. All follow-up BMD measurements were included in the 'ExitBMD' set. Only 155 patients completed 26 cycles (728 days) but not all of these patients provided an exit BMD. In order to analyze data based on patients who had completed the study a 'completer population' was defined. Patients were identified in the data set if they were coded as not having terminated the study and they provided an exit BMD. This distinction provided a completer population of 192 (54.1%) patients (0.025 mg/d – 43; 0.050 mg/d – 48; 0.075 mg/d – 45; and placebo – 56). The mean duration of treatment for the completer population was 730 days (range ———). The Biometrics and Medical reviewers defined the completer population for consistency of their analyses.

Of the 355 patients randomized, 44.8% prematurely terminated participation in the study raising concern that the LOC analysis would not adequately represent the 2-year treatment period. For example, it the majority of patients withdrew prior to Cycle 13 (approximately 1 year) but provided an exit BMD, the LOC analysis would represent a shorter treatment time then planned. To examine this possibility a Survival analysis of early discontinuations was performed with the following results: 192 patients (54.1%) completed the study, 223 patients (63%) completed cycle 13, and 258 patients (73%) were included in the LOC analysis. 'Completers' represented 75% of the patients used in the LOC analysis, therefore it is unlikely that the large patient drop out adversely affected the outcome of the analysis. The Biometrics Reviewer examined the effect of 27% of patients not contributing data to the analysis and found the study result to be robust to the missing data (see Biometrics review).

Watson identified 26 patients (7.2%) as major protocol violators (0.025 mg/d – 4; 0.050 mg/d – 9; 0.075 mg/d – 6; and placebo – 7). Violations included 'abnormal TSH level in patients on thyroid therapy' (7), 'lower than acceptable LS-BMD' (7), 'history of cancer' (3), 'deviations in baseline levels of FSH and estradiol (3), 'abnormal mammogram' (2), 'abnormal laboratory values' (2), 'contraindications to estrogen' (1) and 'disallowed medication (1). Abnormal TSH and low BMD accounted for greater than one-half of the major protocol violations. Since hyperthyroidism is associated with increased bone turnover and can therefore affect BMD, all values were reviewed. Of those patients with abnormal TSH levels, only one had a suppressed TSH. The range for the remaining abnormal values was TSH ——— mIU/l. The BMD range for the protocol violators was ———. In general, these protocol violations equally distributed among the treatment groups and were unlikely to affect the outcome of the study. The inclusion of 14 patients with abnormal lumbar spine radiographs at baseline is discussed in the evaluation of efficacy.

Efficacy

Primary efficacy parameter: the percentage change from baseline in lumbar spine BMD at the end of 2 years.

Lumbar Spine BMD (ITT*)	Estradiol 0.025 mg/day n = 59	Estradiol 0.050 mg/day n = 64	Estradiol 0.075 mg/day n = 63	Placebo n = 72
Baseline				
Mean ± SE	1.054 ± 0.017	1.081 ± 0.018	1.027 ± 0.015	1.041 ± 0.016
Range	[redacted]	[redacted]	[redacted]	[redacted]
End-Point (LOC*)				
Mean ± SE	1.069 ± 0.019	1.118 ± 0.020	1.070 ± 0.015	1.032 ± 0.016
Range	[redacted]	[redacted]	[redacted]	[redacted]
Percent Change Baseline to Endpoint				
Mean ± SE	1.45 ± 0.48	3.39 ± 0.42	4.24 ± 0.49	-0.80 ± 0.45
Range	[redacted]	[redacted]	[redacted]	[redacted]
p-value	0.0018	0.0001	0.0001	

p-value vs. placebo; *ITT = intent-to-treat population, LOC = last-observation-carried-forward

Comment: The data presented by Watson for the primary efficacy outcome was represented to be based on an ITT population (245 patients) at Cycle 26. More correctly, the primary efficacy data should be based on the ITT population with the last-observation-carried-forward (LOC). The LOC analysis should include all patients who were randomized and had ≥ 1 follow-up BMD (this would be 259 patients). Watson excluded 14 patients based on lumbar spine radiographs. All 14 of the excluded patients were noted to have radiographic lumbar spine deformities at baseline and should have been excluded at screening. However, these patients received study drug and were followed long enough to have at least one follow-up BMD and should be included in the LOC analysis. One patient (14701160) was noted to have "fusion with hardware" at baseline and had additional back surgery during the study. This patient was excluded from the LOC analysis because the hardware present would significantly interfere with accurate BMD measurements and could skew the data. This reviewer, with the assistance of the Biometrics reviewer, recalculated the efficacy data using an ITT population of 258 patients (data presented in

preceding table). The Biometrics reviewer confirmed that there was no difference in the outcome of the study using this larger patient population.

Secondary efficacy parameters: the percent change from baseline in lumbar spine BMD at Cycle 13, and the actual change from baseline in lumbar spine BMD at Cycle 13 and Cycle 26.

Lumbar Spine BMD Baseline to Cycle 13 (1-year) (ITT*)	Estradiol 0.025 mg/day	Estradiol 0.050 mg/day	Estradiol 0.075 mg/day	Placebo
Baseline	n= 59	n= 64	n= 63	n= 72
Mean ± SE	1.054 ± 0.017	1.081 ± 0.018	1.027 ± 0.015	1.041 ± 0.016
Range				
End-Point (LOC* to Cycle 13)	n = 53	n = 54	n = 50	n = 65
Mean ± SE	1.070 ± 0.019	1.114 ± 0.022	1.078 ± 0.017	1.034 ± 0.017
Range				
Percent Change Baseline to Endpoint				
Mean ± SE	1.31 ± 0.39	3.47 ± 0.48	4.22 ± 0.42	-0.29 ± 0.45
Range				
p-value	0.014	0.0001	0.0001	

p-value vs. placebo; *ITT = intent-to-treat population, LOC = last-observation-carried-forward

Actual Change in Lumbar Spine BMD (ITT*)	Estradiol 0.025 mg/day	Estradiol 0.050 mg/day	Estradiol 0.075 mg/day	Placebo
Cycle 13 (LOC* to Cycle 13)	n = 53	n = 54	n = 50	n = 65
Mean ± SE	0.014 ± 0.004	0.037 ± 0.005	0.043 ± 0.004	-0.003 ± 0.005
Range				
Cycle 26 (LOC to Cycle 26)	n = 59	n = 64	n = 63	n = 72
Mean ± SE	0.016 ± 0.005	0.037 ± 0.005	0.043 ± 0.005	-0.009 ± 0.005
Range				

*ITT = intent-to-treat population, LOC = last-observation-carried-forward

Lumbar Spine BMD Completer Analysis*	Estradiol 0.025 mg/day	Estradiol 0.050 mg/day	Estradiol 0.075 mg/day	Placebo
Baseline	n = 43	n = 48	n = 45	n = 56
Mean ± SE	1.053 ± 0.021	1.083 ± 0.022	1.046 ± 0.017	1.038 ± 0.018
Range				
Cycle 13 (1-year)	n = 42	n = 47	n = 45	n = 56
Mean ± SE	1.071 ± 0.022	1.119 ± 0.023	1.090 ± 0.017	1.038 ± 0.018
Range				
Percent Change Baseline Cycle 13 (1-year)	n = 42	n = 47	n = 45	n = 56
Mean ± SE	1.59 ± 0.41	3.54 ± 0.49	4.31 ± 0.45	0.04 ± 0.48
Range				
p-value	0.040	0.0001	0.0001	
Cycle 26 (2-years)	n = 43	n = 48	n = 45	n = 56
Mean ± SE	0.020 ± 0.006	0.045 ± 0.005	0.050 ± 0.006	-0.004 ± 0.005
Range				
Percent Change Baseline to Cycle 26 (2-year)	n = 43	n = 48	n = 45	n = 56
Mean ± SE	1.86 ± 0.58	4.08 ± 0.44	4.90 ± 0.60	-0.33 ± 0.53
Range				
p-value	0.031	0.0001	0.0001	

p-value vs. placebo; *Completer = patient who completed the study and contributed Cycle 26 data.

The secondary data show significant difference between all Alora doses vs. placebo at all both Cycle 13 (1-year) and Cycle 26 (2-year) endpoints examined. The treatment effect observed in the completer analysis is similar to that of the ITT analysis.

Comment: As discussed above, the data base included baseline BMD, Cycle 13 BMD, and Exit BMD, but not Cycle 26 BMD. The Cycle 26 BMD data were derived.

C. Efficacy Conclusions

This study compared the effect of three doses of estrogen to placebo on the percent change in LS bone mineral density over a 2-year period in postmenopausal women. All Alora doses tested were found to have statistically significant greater mean percent changes in LS BMDs from baseline to endpoint. This study, however, had several short-comings in design and execution. First, greater than 20% of the patients enrolled would not be considered to be at risk for developing osteoporosis based on a screening BMI ≥ 30 kg/m^2 and T score > -1.0. Second, a number of patients were randomized into the trial who did not meet inclusion/exclusion criteria. For example, fourteen patients were randomized who had vertebral deformities at the time of screening — this would have interfered with accurate BMD measurements. Third, many patients in the study were using herbal and vitamin supplements that may have affected bone metabolism, such as vitamins D and K. And there is no evidence that the contents of these supplements were determined.

As a class, estrogens effectively decrease bone turnover and increase BMD in postmenopausal women. Because estrogen treatment is associated with increased risk of breast cancer, endometrial cancer and venous thrombosis, companies have attempted to identify the 'lowest effective dose'. Other low-dose estrogens have been approved for the prevention of postmenopausal osteoporosis. There is no reason to believe that similar doses of Alora should be less efficacious. The limitations in the study design and execution notwithstanding, subgroup analyses (BMI, time from hysterectomy, previous estrogen use, etc) performed by the Biometrics Reviewer shows that the efficacy results across subgroups are similar to the LOC analysis for the ITT population as a whole.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

In general, safety monitoring for this study was appropriate. The adverse events reported in this 2-year trial were consistent with estrogens as a class with the exception of skin reactions. Skin reactions were reported in > 50% of the patients treated with the Alora transdermal system and were responsible for early withdrawal of 7.9 to 10.1% of estrogen treated patients but no placebo treated patients.

B. Description of Patient Exposure

Three-hundred and fifty-five (355) patients were randomized to the study. Safety analyses included all subjects who received at least one dose of study drug. The mean duration of exposure was 495.6 days (median 722, range [redacted]. All safety variables were summarized in tabular form at each visit for each treatment group.

C. Methods and Specific Findings of Safety Review

Watson has reported the safety results by individual patient and by treatment group. Individual patient data listings are provided in an appendix of the NDA and in the electronic data base. Adverse Events (AEs) are listed by COSTART terms in both the appendix and electronic data bases for all patients, however, Case Report Forms are available for a limited number (22.8%) of patients and are in the electronic data set.

The safety data were reviewed focusing on those AEs that are associated with estrogen use. All serious and unexpected AEs will be outlined. Concomitant medications were reviewed for imbalances among treatment groups.

Safety Assessments

The safety monitoring schedule is as found in the protocol description and included annual mammograms, adverse events monitoring, coagulation factors, carbohydrate metabolism, lipid profile, and other laboratory determinations, and physical examinations. Mammograms were performed at screening and at the Cycle 13 and Cycle 26 (or exit) visits.

Adverse Events

Adverse events during treatment included adverse events which occurred up to 24 hours after the last dose of study drug. Adverse events were reported for a total of 247 patients (92%) in the 3 estradiol treatment groups and for 82 (94%) patients in the placebo group. Most adverse events (94%) were mild or moderate in severity. The majority of adverse events (70%) were considered doubtfully related to study drug by the investigator.

Deaths– Two subjects (Subject 517720 and 5193113), both in the 0.025 mg/day treatment group, reported serious adverse events that led to death. Both events occurred post treatment. Subject 5177120 had liver carcinoma that began 307 days after the start of study drug. Subject 5193113 had a myocardial infarction 673 days after the start of study drug.

Other Serious Adverse Events– Thirty-two (32) subjects (0.025 mg/d – 6; 0.050 mg/d – 6; 0.075 mg/d – 11; and placebo – 9) reported other serious adverse events during the study. Information of the 6 subjects who prematurely terminated because of serious adverse events is summarized in the following table. All subjects discontinued use of study medication.

Serious Adverse Events					
Subject No. (Age)	Days to onset	Preferred term	Investigator term	Severity	Outcome
Estradiol 0.025 mg/day					
14691176 (50)	38	Breast carcinoma	Metastatic breast cancer/stomach cancer	Moderate	Ongoing
	38	Stomach carcinoma	stomach cancer	Moderate	Ongoing
Estradiol 0.075 mg/day					
39051152 (57)	43	Hernia	Right femoral hernia	Severe	Recovered
	65	Hernia	Right femoral hernia exploratory surgery	Severe	Recovered
	75	Thrombosis	Left DVT of leg	Severe	Ongoing
41201133 (57)	563	Carcinoma	Metastatic carcinoma-bone, lungs, liver	Severe	Ongoing
51961075 (56)	386	Breast carcinoma	Carcinoma of left breast	Severe	Recovered
Placebo					
39041284 (48)	15	Cardiomyopathy	Cardiomyopathy of presumed viral etiology	Severe	Recovered
39231016 (59)	485	Spontaneous fracture bone	Fracture right forearm	Severe	Recovered
	485	Spontaneous fracture bone	Fracture right leg	Severe	Ongoing

The incidence of neoplasm-related adverse events are summarized in the following table:

Neoplasm Adverse Events by Treatment Group	Estradiol 0.025 mg/day N=89		Estradiol 0.050 mg/day N=90		Estradiol 0.075 mg/day N=87		Placebo N=87		Overall N=355	
Incidence of Adverse Event	n	%	n	%	n	%	n	%	n	%
Carcinoma	0	0	0	0	1	1.1	0	0	1	0.3
Carcinoma Breast	1	1.1	0	0	1	1.1	0	0	2	0.6
Carcinoma GI	1	1.1	1	1.1	0	0	0	0	2	0.6
Carcinoma Skin	0	0	1	1.1	1	1.1	1	1.1	3	0.8
Neoplasm	1	1.1	0	0	1	1.1	0	0	2	0.6
Neoplasm Breast	3	3.4	5	5.6	1	1.1	6	6.9	15	4.2
Neoplasm Skin	2	2.2	0	0	1	1.1	1	1.1	4	1.1
Neoplasm Urogenital	0	0	1	1.1	0	0	1	1.1	2	0.6
Nodule Skin	1	1.1	1	1.1	0	0	0	0	2	0.6

The most commonly reported neoplasm-related AE was breast neoplasm. The highest percentage was in the placebo group and the lowest percentage was in the 0.075 mg estrogen group, demonstrating no estrogen-related increase in the incidence of breast neoplasm in this study.

Adverse Events leading to premature withdrawal – Fifty-two (52) subjects had adverse events that led to premature withdrawal from the study. The adverse events that were the most frequent reasons for premature termination were application-site reactions (6.8%) and breast pain (1.7%). Twenty-four (24) subjects (estradiol 0.025 mg/day – 7 subjects [7.9%]; 0.050 mg/day – 8 subjects [8.9%]; 0.075 mg/day – 9 subjects [10.1%]; and placebo – 0 subjects) discontinued because of application-site reactions. Six subjects (estradiol 0.025 mg/day – 3 subjects [3.4%]; 0.050 mg/day – 1 subject [1.1%]; 0.075 mg/day – 2 subjects [2.2%]; and placebo – 0 subjects) discontinued because of breast pain. All other adverse events as reasons for premature termination were reported by 1 or 2 subjects per adverse event.

Adverse Events not leading to premature withdrawal – Twenty-eight (28) subjects reported 41 serious adverse events that did not lead to premature termination (estradiol 0.025 mg/day – 7 subjects; 0.050 mg/day – 6 subjects; 0.075 mg/day – 8 subjects; and placebo – 7 subjects).

Incidence of Adverse Events – Adverse events reported in ≥ 5% of patients in any group are reported in the following table. The 5% level is consistent with the current label.

Adverse Events by Treatment Group	Estradiol 0.025 mg/day N=89		Estradiol 0.050 mg/day N=90		Estradiol 0.075 mg/day N=87		Placebo N=87		Overall N=355	
Incidence of Adverse Event	n	%	n	%	n	%	n	%	n	%
Application Site Reaction	47	52.8	51	56.7	49	55.1	51	58.6	198	55.8
Systemic Reactions										
Pain Breast	13	14.6	16	17.8	31	34.8	7	8.0	67	18.9
Respiratory Infection	22	24.7	22	24.4	19	21.3	23	26.4	86	24.2
Arthralgia	5	5.6	10	11.1	11	12.4	12	13.8	38	10.7
Flu Syndrome	8	9.0	12	13.3	97	10.1	9	10.3	38	10.7
Pain Back	5	5.6	3	3.3	6	7.9	5	5.7	20	5.6
Breast Enlargement	1	1.1	2	2.2	6	6.7	3	3.4	12	3.4
Hypertension	3	3.4	3	3.3	6	6.7	3	3.4	15	4.2
Pain	9	10.1	5	5.6	6	6.7	11	12.6	31	8.7
Pruitus	2	2.2	1	1.1	6	6.7	4	4.6	13	3.7
Sinusitis	9	10.1	11	12.2	6	6.7	16	18.4	42	11.8
Headache	10	11.2	8	8.9	5	5.6	11	12.6	34	9.6
Myalgia	3	3.4	2	2.2	5	5.6	4	4.6	14	3.9

Comment: Although the incidence of application site reactions was similar among treatment groups, the severity of the reaction was classified as moderate for more patients in the estrogen treated groups (21.3%, 0.025 mg; 31.4%, 0.050 mg; and 34.7%, 0.075 mg) compared to the placebo group (9.8%). The incidence of breast pain is known to increase in a dose dependent fashion. The increased incidence of hypertension with the higher estrogen dose is also consistent with current labeling for estrogens.

Estrogen Associated Adverse Events – Other AEs known to be associated with estrogen use are summarized in the following table:

Estrogen Associated Adverse Events by Treatment Group	Estradiol 0.025 mg/day N=89		Estradiol 0.050 mg/day N=90		Estradiol 0.075 mg/day N=87		Placebo N=87		Overall N=355	
Incidence of Adverse Event	n	%	n	%	n	%	n	%	n	%
Edema	4	4.5	6	6.7	6	6.9	6	6.9	22	6.2
Weight Increase	3	3.4	2	2.2	5	5.7	6	6.9	16	4.5
Migraine	6	6.7	2	2.2	0	0	2	2.3	10	2.8
Fracture	1	1.1	3	3.3	0	0	7	8.0	11	3.1
All Psychiatric Disorders*	8	9.0	20	22.2	7	8.0	24	27..6	59	16.6
Hot Flushes (Vasodilation)	6	6.7	2	2.2	1	1.1	13	14.9	22	6.2
Thrombosis	0	0	0	0	1	1.1	0	0	1	0.3

*Summary of all Psychiatric Disorders Reported (anxiety, nervousness, emotional liability, insomnia, somnolence, dream abnormalities, depression, confusion)

Comment: All fractures were recorded as 'spontaneous'. A CRF was available for one of these patients. This patient was recorded to have sustained both an arm and leg fracture as a result of a motor vehicle accident. Given the non-specificity of the data recorded, the fracture data is of doubtful use.

Clinical experience has demonstrated that the incidence of hot flushes decreases an increased time from menopause. Therefore, the higher incidence of vasodilation in the placebo group compared to estrogen treatment groups is somewhat unexpected given the time from surgery (and likely menopause) for the majority of patients.

Summary of Adverse Events Reported

Adverse Events by Treatment Group	Estradiol 0.025 mg/day N=89		Estradiol 0.050 mg/day N=90		Estradiol 0.075 mg/day N=87		Placebo N=87		Overall N=355	
Number of Patients Reporting an Adverse Event	n	%	n	%	n	%	n	%	n	%
All Adverse Events	82	92.1	83	92.2	82	92.1	82	92.1	329	92.7
Serious Adverse Events	8	9.0	6	6.7	11	12.4	9	10.1	34	9.6
Application-Site Reaction Adverse Events	47	52.8	51	56.7	49	55.1	51	58.6	198	55.8
Adverse Events as Reasons for Premature Termination	14	15.7	12	13.3	20	22.5	6	6.9	52	14.6

Concomitant Medications

Concomitant medications by drug class for each treatment group were provided in tabular form. Medications started during the study were not reported separately but were included in the list of medications used by individual patients. Medications started in response to AEs events were reported in tabular form by drug class.

Comment: In general, there were no clinically significant imbalances in the concomitant medications among the treatment groups. Approximately 50% of patients used some form of vitamin supplement. As discussed in the Study Medication section the components of these supplements was not well described. More patients receiving estrogen treatment (all doses) than placebo required corticosteroids (dermatological preparations). This is consistent with the higher incidence of premature termination in these treatment groups.

Clinical Laboratory Evaluation

Hematology and clinical chemistry data, including serum lipid profile and carbohydrate metabolism parameters, were collected at screening and after cycles 7, 13, 20, and 26. Parameters that were followed included means and shifts and grade changes at each time point.

For changes from baseline in mean laboratory values, there were no significant changes in hematology or chemistry values. For hematology, this included hemoglobin, hematocrit, RBC, WBC and platelet counts. For serum chemistries, values included sodium, potassium, bicarbonate, chloride, and creatinine. For liver function tests, values included alkaline phosphatase, GGTP, AST, ALT and total bilirubin. Other tests include calcium, albumin, and phosphorus.

The number of patients with laboratory value shifts from normal (at baseline) to abnormal (high or low) post-baseline are generally similar among the treatment groups. Those shift frequencies that occurred in ≥ 5% of the patients are summarized in the following table:

Laboratory Value Shifts at exit by Treatment Group	Estradiol 0.025 mg/day N = 89 N*= 61		Estradiol 0.050 mg/day N = 90 N*= 72		Estradiol 0.075 mg/day N = 87 N*= 65		Placebo N = 87 N*= 75		Normal Range
Number of patients with shifts from normal to high or low	n	%	n	%	n	%	n	%	
Chloride (mEq/L) high	4	6.6	3	4.2	1	1.5	0	0	9.5-108 meq/l
GGTP (IU/L) high	1	1.6	2	2.8	7	10.8	3	4.0	0-45 IU/l
Phosphorus (mg/dl) high	4	6.6	2	2.8	4	6.2	7	9.3	2.5-4.5 mg/dl
PT (sec) low	30	50.8	40	56.3	33	53.2	35	50.0	10.0-12.5 sec
PTT (sec) low	6	10.2	9	12.7	6	9.7	10	14.3	24.0-36.0 sec
HBA_{1c} (%) high	4	6.7	2	2.8	5	7.8	5	6.8	< 6.5%
Cholesterol (mg/dl) high	5	8.2	5	6.9	7	10.8	1	1.3	<200 mg/dl
LDL (mg/dl) high	5	8.2	6	8.3	5	7.7	4	5.3	<130 mg/dl
Triglycerides (mg/dl) high	8	13.1	2	2.8	1	1.5	5	6.7	<200 mg/dl

N*= number of patients contributing data at time point

Comment: None of these results is clearly related to estrogen use. The increase in GGTP was seen with the highest dose of estrogen — the clinical significance of this is unclear given that transdermal delivery negates the first pass effect seen with oral estrogens. Increases in lipid values are difficult to interpret because the exclusion of patients with lipid abnormalities was changed as an addendum to the protocol. Since it is not clear whether these changes are related to estrogen use or to changes in concomitant medications, clinical significance can not be defined.

Vital Signs

Summary statistics were provided for blood pressure and heart rate. As noted in the summary of adverse events, hypertension was seen in the 0.075 mg/day estrogen treatment group. No other abnormalities were reported among the groups.

Mammography

There were no clinically important changes in mammographic findings in any treatment group from baseline. From 17 to 21% of patients had abnormalities of the left breast and 17 to 19% of the right breast at screening. Of those patients with changes from baseline, most had a worsening of the mammogram results (Left: 0%, 0.025 mg; 8.5%, 0.050 mg; 3.7%, 0.075 mg; and 1.6%, placebo. Right: 4%, 0.025 mg; 6.8%, 0.050 mg; 1.9%, 0.075 mg; and 1.6%, placebo.) Those patients diagnosed with breast neoplasms are outlined above.

D. Summary of Safety Findings and Limitations of Data

The safety profile appears to be consistent with other marketed estrogens. The formulation was changed during the course of the trial. It appears that the formulation used for the study is not the formulation for which Watson is requesting approval. Although the supplemental NDA submission to DRUDP demonstrated bioequivalence of the new formulation the maximum exposure appears to be 96 hours. There are no studies for the new formulation in this NDA. Approximately one-half of the patients enrolled in the study experienced skin irritation from the patch. It would be concerning if the new formulation caused an increase in this adverse event. An additional limitation of the Alora transdermal system is that

VIII. Dosing, Regimen, and Administration Issues

IX. Use in Special Populations

Alora is indicated for use by postmenopausal women and therefore not indicated for use in males, children (a pediatric waiver was requested) or pregnant women.

The majority (86.5%) of the subjects in this study were white. Osteoporosis is generally a condition of thin, white or Asian women. There is insufficient clinical information available to make recommendations for other populations.

The safety and effectiveness in geriatric patients (over age 65) have not been established (current labeling). This is concerning since estrogens are prescribed to many patients in this age group for prevent and treatment of osteoporosis. While some patients enrolled in this study were ≥ 65 years of age, the study was not designed to specifically address safety and efficacy in this population.

X. Conclusions and Recommendations

A. Conclusions

This 2-year study conducted by Watson Laboratories demonstrates that 0.025, 0.05, and 0.75 ug/day of transdermal estrogen increase LS BMD in a dose-dependent and by a statistically significantly greater extent than placebo in postmenopausal women without uteri. The safety profile of Alora appears to be similar to other estrogens.

B. Recommendations

Approval pending agreement with Watson on final product labeling.

XI. Appendix (Proposed Labeling)

Annotated version of proposed labeling changes with Reviewer's comments.

Estradiol Matrix
Transdermal Delivery System

Annotated Package Insert

May 9, 2001

Watson Laboratories Inc.
Research Park
417 Wakara Way
Salt Lake City, UT 84108 USA

Note: Labeling changes from the Medical reviewer are incorporated into the body of the text. When indicated, comments related to the changes appear in text boxes and are not to be incorporated into the label.

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Labeling

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/s/

Patricia Beaston-Wimmer
11/2/01 04:39:39 PM
MEDICAL OFFICER

Eric Colman
11/7/01 11:40:46 AM
MEDICAL OFFICER

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-310

CHEMISTRY REVIEW(S)

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-310

DATE REVIEWED: 10/25/01

REVIEW #: 1

REVIEWER: Elsbeth G. Chikhale

SUBMISSION TYPE	DOCUMENT DATE
ORIGINAL	1/12/01
AMENDMENT	10/19/01
FAX COMMUNICATION	10/23/01

NAME & ADDRESS OF APPLICANT:

Watson Laboratories, Inc.
Research Park
417 Wakara Way
Salt Lake City, UT 84108

DRUG PRODUCT NAME

Proprietary: Alora® Transdermal system
Established: Estradiol transdermal system
Code Name/#: [redacted]
Chem.Type/Ther.Class: 3 S

PHARMACOL. CATEGORY/INDICATION: Estrogen, hormone replacement therapy/indicated for the prevention of osteoporosis in post-menopausal women.

DOSAGE FORM: Transdermal Delivery System (3-4 day application)

STRENGTHS: Same formulation composition, four different surface areas:
0.75 mg, delivery rate 0.025 mg/day, surface area 9 cm^2
1.5 mg, delivery rate 0.05 mg/day, surface area 18 cm^2
2.3 mg, delivery rate 0.075 mg/day, surface area 27 cm^2
3.0 mg, delivery rate 0.1 mg/day, surface area 36 cm^2

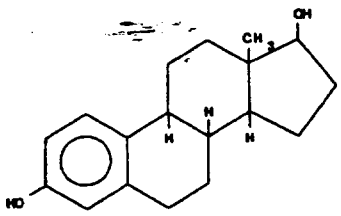
ROUTE OF ADMINISTRATION: Transdermal

Rx/OTC: x Rx ____ OTC

SPECIAL PRODUCTS: ____ yes x no

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

Estra-1,3,5(10)-triene-3,17β-diol
$C_{18}H_{24}O_2$, Mol. Wt. 272.39



REMARKS: Alora®, is an estradiol containing transdermal delivery system (patch) that is designed to deliver estradiol through the skin in a

continues manner, over a period of 3-4 days. Three strengths of Alora® drug product have been approved since 1996 by the division of Reproductive and Urologic Drug Products (DRUDP), HFD-580, for the indication of hormone replacement therapy in post menopausal women. Per FDA request, a new NDA (21-310) is filed to this Division (HFD-510) in stead of a supplement to the already approved NDA (20-655), for the approval of all approved strengths and a new strength — mg) indicated for the prevention ——— of postmenopausal osteoporosis. ——— is manufactured by ——— Detailed information regarding the ——— has been submitted as Type II DMFs by ——— . The drug substance for the new strength drug product is identical to the currently approved product (3 strengths of Alora® Transdermal System, NDA 20-655). The referenced DMFs have been previously reviewed and found adequate to support NDA 20-655, thus the CMC information is also adequate to support this NDA. The new ' — mg) strength is a 9 cm^2 patch containing the exact identical formulation and transdermal delivery system, with a proportionally reduced patch size, as the three strengths approved by DRUDP. Amendment dated 10/19/01 provided for EIC (Expected Introduction Concentration) and for clarification on the use of ——— in the drug product formulation. EERs were filed with the office of compliance for both the manufacturers of ——— and the manufacturer of the drug product (Watson Laboratories, Inc.) and the facilities were found acceptable on 3-16-01, 3-8-01, and 3-20-01 respectively (see attached EES printout). An OPDRA consult for the trade name was not required since the product is already on the market with the trade name Alora.

CONCLUSIONS & RECOMMENDATIONS:

From chemistry standpoint, the NDA can be approved. The applicant should be reminded that only the drug products (4 strenths) containing ——— ——— are approved for marketing, as indicated in the firms amendment dated 10/19/2001. In the package insert, the MW should be changed to 272.39 instead of ———

cc:
Org. NDA 21-310
HFD-510
HFD-510/EGChikhale
HFD-510/SWu
HFD-510/DGWu/

R/D Init by:

Filename: 21310

Elsbeth G. Chikhale, Ph.D.
Review Chemist

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Duu-gong Wu
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CHEMIST
Check-in for E. Chikhale

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-310

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA 21-310
Review number: 1
Information to sponsor: Yes (X) No ( )
Sponsor and/or agent: Watson Laboratories Inc., Salt Lake City, UT

[redacted]

Reviewer: Karen Davis-Bruno
Division name: DMEDP
HFD #: 510
Review completion date: 5/11/01

Drug:

Trade name: Alora
Generic name: [redacted] estradiol [redacted]
transdermal delivery system
Code name: [redacted]
Chemical name: estra-1,3,5(10)-triene-3,17β-diol [redacted]

CAS registry number: 50-28-2 (estradiol) [redacted]
Molecular formula/molecular weight: $C_{18}H_{24}O_2$ MW=272.39 (estradiol), [redacted]

Relevant INDs/NDAs/DMFs: [redacted] NDA 20-655 (HFD-580) [redacted]

Drug class: [redacted] estrogen [redacted]

Indication: prevention [redacted] of postmenopausal osteoporosis

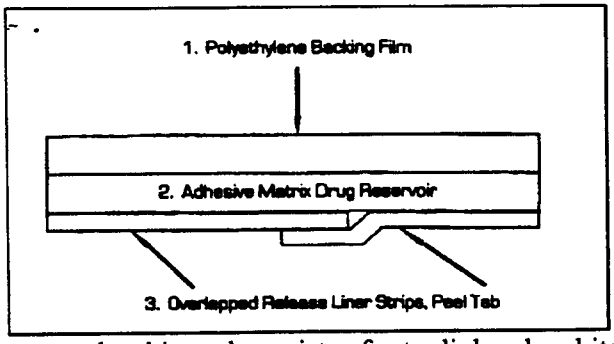
Clinical Dose: Three dosage strengths of Alora: 0.05, 0.075 and 0.1 mg/day are marketed with NDA 20-655 approved for treatment of moderate to severe vasomotor symptoms associated with menopause. A new dosage strength of 0.025 mg/day is being requested for the osteoporosis indication. The patch is applied every 3-4 days an alternate sides of the abdomen.

Clinical Experience: A 2 year multicenter, double blind, double dummy randomized placebo controlled parallel group study in 330 hysterectomized, non osteoporotic women with doses of 0.025, 0.05 and 0.075 mg/day Alora. All pateints received 1000 mg oral elemental calcium.

Drug Product:

Delivery Rate *in vivo*	Estradiol Content (mg)	Contact Surface (cm^2)
0.025	0.75	9
0.05	1.5	18
0.075	2.3	27
0.1	3	36

The Alora system consists of three layers from the polyethylene backing film, the adhesive



matrix drug reservoir contacts the skin and consists of estradiol and sorbitan monooleate dissolved in an acrylic adhesive. The polyester release liner protects the adhesive matrix during storage and is removed prior to use.

Route: **transdermal**

OVERALL SUMMARY AND EVALUATION: This NDA application is for an approved product at new lower dose for new osteoporosis indication, preclinical information has not been provided. NDA 20-655 was reviewed previously by DRUDP HFD-580 and is used to reference preclinical data. Pharmacology recommends approval with labeling changes indicated below.

Communication review:

Labeling review: Pregnancy Category X : [redacted] should not be used during pregnancy [redacted]

RECOMMENDATIONS:

External recommendations (to sponsor): Please revise the draft labeling for section F. Pregnancy Category as follows: Pregnancy Category X: [redacted] should not be used during pregnancy [redacted]

Reviewer signature: [redacted]

cc: HFD510/Davis-Bruno/

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/s/

Karen Davis-Bruno
5/14/01 11:49:28 AM
PHARMACOLOGIST

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-310

STATISTICAL REVIEW(S)

Statistical Review and Evaluation[1]

NDA:	21-310
Sponsor:	Watson Labs
Drug:	Alora (estradiol transdermal systems)
Indication:	Prevention ——— of postmenopausal osteoporosis
Materials reviewed:	Hard copy submission stamp dated 1/16/01 (vol, 1.1, 1.22-1.37) and data in electronic document room
Medical Reviewer:	Patricia Beaston-Wimmer, M.D., Ph.D. (HFD-510)

The sponsor submitted data from one randomized, double-dummy, placebo controlled, 2-year, multicenter trial to support the use of Alora (estradiol) in the prevention ——— of postmenopausal osteoporosis (Table 1). The trial randomized hysterectomized (with or w/o bilateral oophorectomy) postmenopausal women <70 years of age in equal numbers to three doses of Alora (.025 mg/day, .05 mg/day and .075 mg/day) and placebo. Women with prior estrogen use had a washout period of 2 months prior to randomization. The study treatment consisted of twice-weekly applications of 9 and 18 cm^2 patches (active and placebo) applied to the lower abdomen for twenty-six 28-day cycles. All subjects received 1000mg/day of oral calcium.

Table 1. Trial design

Study/# centers	Population	Treatment groups (# randomized)	Duration
1996023 22 US	Postmenopausal women Age <70 yrs Lumber spine BMD by —— >0.772g/cm^2 on ——— or >0.882g/cm^2 on ———	Placebo (87) Estradiol .025 mg/day (89) Estradiol .05 mg/day (90) Estradiol .075 mg/day (89)	2 years (twenty-six 28-day cycles)

The objective of the trial was to establish the minimally effective dose that significantly prevents lumbar spine bone loss as measured by bone mineral density (BMD) when compared to placebo. BMD was measured at the lumbar spine only.

Study periods consisted of Screening, Baseline (within 28 days of Screening) and Treatment. Patient visits were scheduled at Screening and after (Treatment) Cycles 1, 3, 5, 7, 10, 13, 16, 20, 23 and 26.

The protocol-specified primary endpoint was % change from baseline in lumber

[1] Key words: clinical studies, NDA review, one study application, missing data

spine BMD at 2 years. Lumbar spine BMD was measured at Screening, Cycle 13 and Cycle 26 (last visit). Patients dropping prior to their scheduled Cycle 26 visit were required by protocol to have an exit lumbar spine BMD measurement. Secondary efficacy parameters were % change in lumbar spine BMD at Cycle 13 and actual change in lumbar spine BMD at Cycles 13 and 26.

BMD measurements were obtained on either [redacted] machines. The machines provide different BMD measurements. In order to make the baseline readings from the machines comparable, raw BMD measurements were standardized using the following algorithm:

standardized BMD = 1.0755 • BMD [redacted]
= 0.9522 • BMD [redacted]

The primary endpoint (BMD % change) is the same for both the raw and standardized measurements.

Results

Baseline and demographic data for all randomized patients are shown in Table 2. The mean age of patients was 53 years. Most patients were Caucasian (86%). Groups were well balanced (no statistically significant differences) with respect to all variables in Table 2 and (not shown in Table 2) BMD t score at baseline.

Table 2. Baseline and demographic data

	Placebo (n=87)	Est .025 (n=89)	Est .05 (n=90)	Est .075 (n=89)	Total (n=355)
Age (yrs)					
Mean (SD)	54 (7)	52 (8)	54 (7)	54 (7)	53 (7)
Median	54	52	53	54	54
(Min, Max)	(26, 68)	(29, 69)	(30, 69)	(36, 69)	(26, 69)
Weight (lbs)					
Mean (SD)	162 (31)	171 (38)	166 (34)	170 (36)	167 (35)
Median	161	164	163	165	163
(Min, Max)	(100, 263)	(95, 281)	(100, 255)	(103, 307)	(95, 307)
Height (in)					
Mean (SD)	64 (2)	64 (3)	64 (2)	64 (2)	64 (2)
Median	65	65	64	65	65
(Min, Max)	(60, 69)	(57, 70)	(60, 69)	(59, 70)	(57, 70)
Race					
Caucasian	74 (85%)	78 (88%)	76 (84%)	79 (89%)	307 (86%)
Black	6 (7%)	6 (7%)	7 (8%)	6 (7%)	25 (7%)
Hispanic	5 (6%)	3 (3%)	4 (4%)	1 (1%)	13 (4%)
Other	2 (2%)	2 (2%)	3 (3%)	3 (3%)	10 (3%)
Tobacco use					

Table 2, cont. Baseline and demographic data

Never used	41 (47%)	35 (39%)	51 (57%)	36 (40%)	163 (46%)
Previously used	24 (28%)	26 (29%)	23 (26%)	28 (31%)	101 (28%)
Currently use	22 (25%)	28 (31%)	16 (18%)	25 (28%)	91 (26%)
Alcohol use					
Never used	22 (25%)	19 (21%)	23 (26%)	25 (28%)	89 (25%)
Previously used	5 (6%)	13 (15%)	8 (9%)	14 (16%)	40 (11%)
Currently use	60 (70%)	57 (64%)	59 (66%)	50 (56%)	226 (64%)
Bilateral oophorectomy					
Yes	43 (49%)	47 (53%)	46 (51%)	49 (55%)	185 (52%)
No	44 (51%)	41 (46%)	44 (49%)	40 (45%)	169 (48%)
N/A	0	1 (1%)	0	0	1 (<1%)
Mean BMD (g/cm^2)	1.05	1.04	1.07	1.04	1.05
Mean yrs since hysterectomy	16.2	15.7	15.5	16.9	16.1

Patient disposition

355 patients were randomized and received study drug. Table 3 shows the number of patients on study at the scheduled visit times. One hundred ninety six (196) patients (55%) completed the study. The completion rate was highest in the placebo group (67%), at least 13% higher than the completion rates in the Alora dose groups.

Table 3. Patients on study

# patients completing	Placebo	Est .025	Est .05	Est .075	Total
Baseline	87 (100%)	89 (100%)	90 (100%)	89 (100%)	355 (100%)
Cycle 1	85 (98%)	83 (93%)	85(%)	81(91%)	334(94%)
Cycle 2	82 (94%)	82 (92%)	80(%)	79(89%)	323(91%)
Cycle 3	80 (92%)	78(88%)	72(%)	71(80%)	301(85%)
Cycle 5	75 (86%)	70(79%)	68(%)	66(74%)	279(79%)
Cycle 7	70 (80%)	64(72%)	66(%)	63(71%)	263(74%)
Cycle 10	69 (79%)	60(67%)	59(%)	56(63%)	244(69%)
Cycle 13	65 (75%)	55(62%)	56(%)	51(57%)	227(64%)
Cycle 16	61 (70%)	50(56%)	53(%)	47(53%)	211(59%)
Cycle 20	58 (67%)	46(52%)	52(%)	46(52%)	202(57%)
Cycle 23	58 (67%)	45(51%)	50(%)	45(51%)	198(56%)
Cycle 26 (completers)	58 (67%)	44 (49%)	49 (54%)	45 (51%)	196 (55%)
Endpoint	72 (83%)	60 (67%)	64 (71%)	63 (71%)	259 (73%)

The difference in completion rates between placebo and the Alora dose groups was due primarily to the greater number of dropouts due to adverse reactions, particularly application site reactions (Table 4).

Table 4. Reasons for discontinuation

	Placebo (n=87)	Est .025 (n=89)	Est .05 (n=90)	Est .075 (n=89)	Total (n=355)
AE					
Appl site reaction	0	7	8	9	24
Other	6	7	4	11	28
Inv recommendation	0	1	2	0	3
Prot violations					
Incl criteria	0	0	1	0	1
Excl criteria	1	0	3	0	4
Non-compliance					
Dose schedule	0	0	0	1	1
Visit Schedule	2	4	3	0	9
Excl concom meds	0	1	0	1	2
Voluntary w/d	12	15	13	11	51
Lost to follow-up	8	8	7	11	34
Death	0	2	0	0	2
Total discontinued	29	45	41	44	159

As stated previously, patients dropping prior to Cycle 26 were required by protocol to have a lumbar spine BMD measurement at exit. Table 5 describes the endpoint data. The nature of the endpoint data depended on completion status and, if the patient dropped from the study, time of dropout.

It is important to note that one hundred twenty eight (128) patients dropped prior to their scheduled Cycle 13 visit, but only 32 patients (25% of 128) received exit lumber spine BMDs as required by protocol. The other 96 patients (75% of 128) did not receive an exit lumber spine BMD measurement and therefore did not contribute data to an endpoint analysis. Patients dropping after the scheduled Cycle 13 visit all furnished endpoint data, either as exit BMD data or the Cycle 13 BMD measurement.

Table 5. Description of endpoint data

Patient status	Data used as endpoint	Number of pts (%)
Completers	Cycle 26 [1]	196 (55%)
Dropouts		
Before Cycle 13	Exit BMD	32 (9%)
	None [2]	96 (27%)
After Cycle 13	Exit BMD	10 (3%)
	Cycle 13	21 (6%)
Total		355 (100%)

[1] Three patients completed the study but had no data for Cycle 26. Their Cycle 13 data were used as endpoint data.

[2] These 96 patients (27%) did not contribute data towards an endpoint analysis

The sponsor's ITT population was defined as the set of all randomized subjects with on-treatment data but excluded 14 patients who had vertebral deformities (n=245). This definition was applied to analysis populations which used substantially fewer than 245 patients. For example, several ITT analyses actually consisted of observed cases data. The set of evaluable patients consisted of patients with data who were compliers and did not have major protocol violations.

No single statistical analysis performed by the sponsor used more than 69% of the total number of randomized subjects.

As mentioned above, all of the sponsor's statistical analyses omitted data from 14 patients with vertebral deformities (4, placebo; 3, .025mg; 6, .05mg; 1, .075mg). Vertebral deformities were an exclusion criterion in the protocol: a subject could be excluded from the study if she had "severe fracture deformation that would preclude precise measurements as determined by the radiographic screening facility". All 14 patients had vertebral deformities at baseline based on x-ray, however, no follow-up (on-treatment) x-rays were performed. In consultation with the medical reviewer, this reviewer excluded from statistical analysis only one of the 14 patients with vertebral deformities. The excluded patient (#14701160) was the only patient with a documented spinal fusion with hardware and had a 116% change in BMD from baseline at endpoint. The statistical results including and excluding the other 13 patients were similar.

Not Right Fine Method

Prior to breaking the code, the sponsor changed the statistical analysis from Fisher's LSD to Dunnett's. Of the two multiple comparison procedures, Dunnett's is the preferred procedure since Fisher's LSD does not control the familywise error rate for greater than three treatment groups. The Dunnett's alpha for each of the 3 pairwise comparisons between Alora and placebo is α=0.019. This alpha level is slightly less conservative than the Bonferroni level α=0.017. The statistical model was ANOVA with terms for treatment and center.

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Table 6 shows statistical results for the primary endpoint. Figures 1 and 2 show BMD values over time for completers. The aforementioned Patient #14701160 who received .025mg/day was omitted from the graph. For the Cycle 26 endpoint data, all Alora doses were statistically superior to placebo on the primary endpoint.

Table 6. Results for lumbar spine BMD
ITT dataset (n=258)

	Placebo (n=72)	Est .025 (n=59)	Est .05 (n=64)	Est .075 (n=63)
Baseline mean	1.041	1.054	1.081	1.027
Mean endpoint [1]	1.032	1.069	1.118	1.070
Mean % change from baseline				
Cycle 13 OC [2]	-0.3% (n=65)	1.3% (n=53)	3.5% (n=54)	4.2% (n=50)
Cycle 26 OC [2]	-0.3% (n=56)	1.9% (n=43)	4.1% (n=48)	4.9% (n=45)
Cycle 26 endpoint [1]	-0.8%	1.4%	3.4%	4.2%
Difference vs placebo (cycle 26 endpoint)				
Mean		2.3%	4.2%	5.0%
Least squares mean [3]		2.1%	4.1%	5.0%
p-value [3]		p=.0018 [4]	p=.0001 [4]	p=.0001 [4]

[1] endpoint = last observation carried forward

[2] OC = observed cases. The sponsor did not explicitly include Cycle 26 data in the electronic database. Patients listed as completing the trial and providing exit data were included in the Cycle 26 data.

[3] from ANOVA with treatment and center as factors. Per protocol, sites that had not recruited at least 8 subjects were to be pooled on the basis of geographic region for assessing the treatment-by-center interaction effect. The sponsor combined the 22 centers into 6 pooled centers although there were only 3 small centers (#3913, n=3; #4172, n=5; and #4647, n=2). Since the primary purpose of pooling was to carry out the test of interaction, which was not statistically significant, and there were only 3 centers with fewer than 8 recruited patients, this reviewer considered pooling to be unnecessary. The 'center' term in the model represents the unpooled data.

[4] Statistically significant by Dunnett's test (α=0.019)

Missing data

Ninety seven (27%) randomized subjects did not have on treatment data and so did not contribute to the endpoint analysis. This percentage is high but comparable with other data from trials of other estradiols: Climara (24%), Vivelle (30%) and Activella (2 trials; 21% and <20%). Still, the high % of missing data may have impacted the results of the trial. To investigate the sensitivity of the results to missing data, this reviewer performed a type of worst-case analysis similar to one suggested by Dr. Johnson, the medical reviewer for NDA 20-905 (HFD-550, ARAVA for the treatment of active rheumatoid

arthritis), and carried out by the statistical reviewer, Dr. Lu (HFD-720). The statistical approach is formulated to answer the following question: What is the smallest effect size one could impute for the missing data and still retain statistical significance for the all-randomized dataset (n=355)?

The Appendix shows calculations at two Type I error rates, α=0.05 and α=0.019, comparing the low dose and placebo on the primary endpoint. The more relevant calculation is the one involving α=0.019 since this alpha level accounts for the multiple comparisons with placebo. The mean responses (observed and imputed) for the 2 groups were:

+1.25%	Alora observed
+0.37%	Placebo missing (imputed)
+0.05%	Alora missing (imputed)
-0.83%	Placebo observed

The imputed values in the Alora and placebo missing data cohorts were +0.05% and +0.37, respectively. Therefore, the missing cohort could have a treatment difference as large as -0.32% (the negative sign indicates the treatment difference favors placebo) and still maintain a statistically significant difference between groups. Note that the imputed placebo (Alora) response is closer to the Alora (placebo) observed response than to the placebo (Alora) observed response.

Overall, the results appear to be robust to the missing data.

The procedure could also be carried out for the Alora .05mg and .075mg groups. However, this is unnecessary since the deltas for these groups were larger than the delta for the .025mg group (which has been shown to be robust) and the amount of missing data in the dose groups is similar.

Covariates

The following covariates were analyzed with respect to their effect on treatment: age, race, previous estrogen use, baseline lumbar spine T score, years since hysterectomy, and BMI. The latter variable was suggested by the FDA Medical reviewer. Graphs 3-8 show boxplots of endpoint BMD data for each treatment group stratified by the covariate of interest. Continuous variables (age, t score, years since hysterectomy and BMI) were stratified by the [redacted] value.

The sponsor analyzed subgroups by generating separate p-values for each subgroup. This method is generally inappropriate for examining subgroup differences. This analysis can be misleading when p-values for different subgroups fall above and below .05 giving the impression that the drug works in one subgroup and not in another. This was the case for several subgroups (baseline t score, previous estrogen use, years since hysterectomy)

where the low-dose was judged to be significant in one subgroup but not significant in the other subgroup.

This reviewer analyzed each subgroup using a single statistical model applied to the entire dataset. The model included factors for treatment, subgroup and an interaction term (treatment-by-subgroup) which was evaluated at the 0.10 level of significance. Each dose was compared to placebo in a separate analysis.

This reviewer found three nominally significant interactions with treatment. The interactions were all quantitative in nature. None of these interactions would remain statistically significant at the .10 level if multiplicity from subgroups and doses were taken into account:

- Patients having hysterectomies at least 16-1/2 years prior to trial entry had larger treatment differences (low dose vs placebo) than patients having more recent surgeries (p=.10).

- Patients with high (above median) baseline t scores had greater treatment differences (low dose vs placebo) than patients with lower t scores (p=.085)

- Patients having previously taken estrogen had larger treatment differences (high dose vs placebo) than patients who had not taken estrogen (p=.06)

Input from the FDA medical reviewer is needed to determine how compelling these subgroup differences are from a clinical standpoint.

Fracture data

Fracture was a safety endpoint. Eleven (11) patients experienced a fracture during the trial, seven in the placebo group and 4 in the combined Alora groups.

Labelling considerations

1. Treatment effects were about the same for the ITT/endpoint and completer populations. Either present endpoint data in a table, or curves over time for completers. The graph could also show endpoint data separate from the completers.
2. Show by-treatment sample sizes; the label mentions only the overall sample size.
3. The sponsor claims each dose of Alora is effective at all timepoints.

   [redacted] Displaying the primary endpoint data over time should be sufficient to give prescribers information about the drug's onset of action.

Summary and conclusions

For the ITT dataset, all doses of Alora (.025, .05 and .075mg/day) produced statistically significant changes in lumbar spine BMD compared to placebo at 2 years. These differences were robust with respect to adjustments for multiple comparisons with placebo, and missing data.

J. Todd Sahlroot, Ph.D.
Mathematical Statistician

Concur: Dr. Nevius

Cc:
NDA 21-310
HFD-510/SWu, EColman, PBeaston-Wimmer
HFD-715/ENevius, TSahlroot
HFD-700/CAnello

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APPENDIX

Question: What is the smallest effect size one could impute for the missing data and still retain statistical significance for the all-randomized dataset (n=355)? Compare the lowest Alora dose .025mg/day (A) and placebo (P) using the endpoint (lumbar spine % change) data (n=258)

Methods

Let
- y_A = observed mean response in the Alora group
- y_P = observed mean response in the placebo group
- n_A = total sample size in the Alora group
- n_P = total sample size in the placebo group
- n_{AO} = sample size in the observed Alora cohort
- n_{PO} = sample size in the observed placebo cohort
- n_{AM} = sample size in the missing Alora cohort
- n_{PM} = sample size in the missing placebo cohort
- $y_A - \Delta$ = mean response in the Alora missing group
- $y_P + \Delta$ = mean response in the placebo missing group

where Δ is the increment (decrement) in the imputed response for the placebo (Alora) missing cohort with respect to the observed data.

The overall treatment difference $D(\Delta)$

$$= (n_{AO}y_A + n_{AM}(y_A - \Delta))/ n_A - (n_{PO}y_P + n_{PM}(y_P + \Delta))/ n_P$$

$$= (y_A - y_P) - \Delta(n_{AM}/ n_A + n_{PM} / n_P)$$

The SE of $D(\Delta)$ is the usual 2-sample or pooled estimate using the observed SD and the total sample sizes n_A and n_P. SE(D) does not depend on Δ.

Calculate Δ such that $Z_{\alpha/2} = D(\Delta) / SE(D)$.

Solving for Δ yields:

$$\Delta = [(y_A - y_P) - Z_{\alpha/2} \bullet SE(D)] / (n_{AM}/ n_A + n_{PM}/ n_P]$$

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Results

	Sample sizes			LS mean [1]	SD[2]
	Observed	Missing	total		
Alora	$n_{AO} = 59$	$n_{AM} = 30$ [3]	$n_A = 89$	$y_A = +1.25$	SD = 3.86
Placebo	$n_{PO} = 72$	$n_{PM} = 15$	$n_P = 87$	$y_P = -0.83$	SD = 4.39

[1] Least square means taken from SAS printout
[2] SD(Alora) = SE(LSM) • sqrt(n_{AO}). (SE(LSM) = .5023 taken from SAS printout.)
SD(Placebo) = SE(LSM) • sqrt(n_{PO}). (SE(LSM) = .5175 taken from SAS printout.)
[3] One Alora patient with data (endpoint=116%) was coded as missing

$$SE(D) = \text{sqrt}[\ (88)(3.86)^2 + 86(4.36)^2\ ]/\text{sqrt}(174) \bullet \text{sqrt}(1/89 + 1/87)$$
$$= 0.62$$

$$\Delta = [(1.25 + 0.83) - 1.96 \bullet SE(D)] / [\ (89 - 59)/89 + (87 - 72)/87\ ]$$
$$= 1.70$$

$$y_A - \Delta = 1.25 - 1.70$$
$$= -0.45$$
$$y_P + \Delta = -0.83 + 1.70$$
$$= +0.87$$

Therefore, the missing cohort could have a treatment difference as large as D* satisfying

$$D^* = (y_A - \Delta) - (y_P + \Delta)$$
$$= y_A - y_P - 2\Delta$$
$$= -1.32\% \text{ (favoring placebo)}$$

and still maintain a nominally statistically significant difference between groups (p=.05) for the all-randomized dataset.

To adjust for 3 multiple comparisons with placebo, use a Dunnett's correction ($\alpha = .019$, $Z_{\alpha/2} = 2.35$). Reworking the calculations and replacing 1.96 by 2.35 gives Δ=1.20 and D* = -0.32 (favoring placebo).

Figure 1
mean lumber spine BMD (g/cm2)

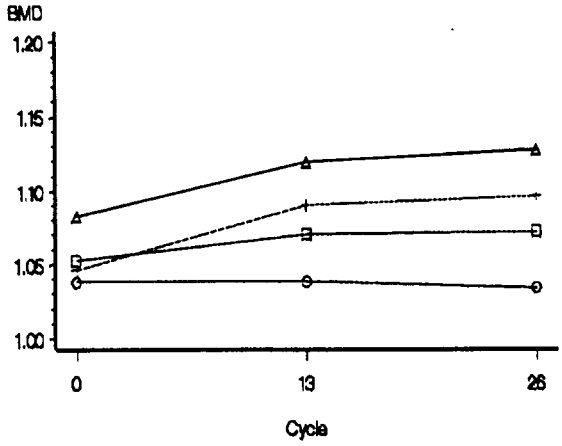

Figure 2
lumber spine BMD
mean % change from baseline

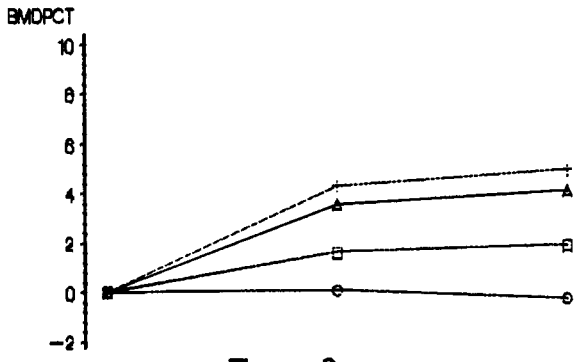

Figure 3
Trial 1996023
% change in lumber spine BMD by age
AGE= age 55 or older

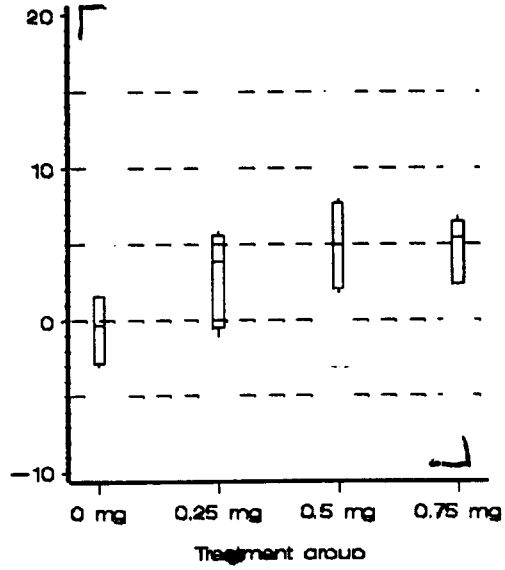

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Figure 3
Trial 1996023
% change in lumbar spine BMD by age
AGE= age 55 or older

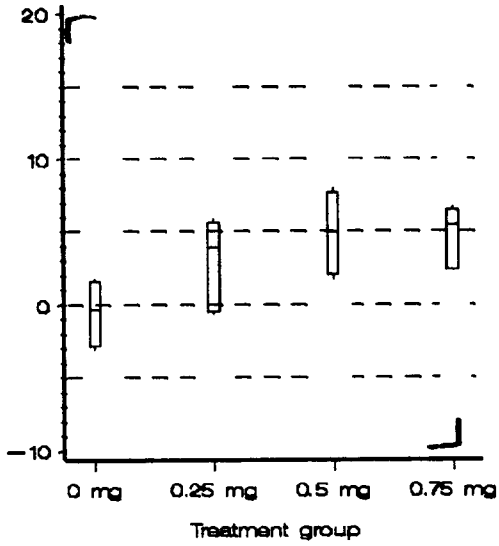

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Figure 4
% change in lumbar spine BMD by race
Ethnic code= BLA

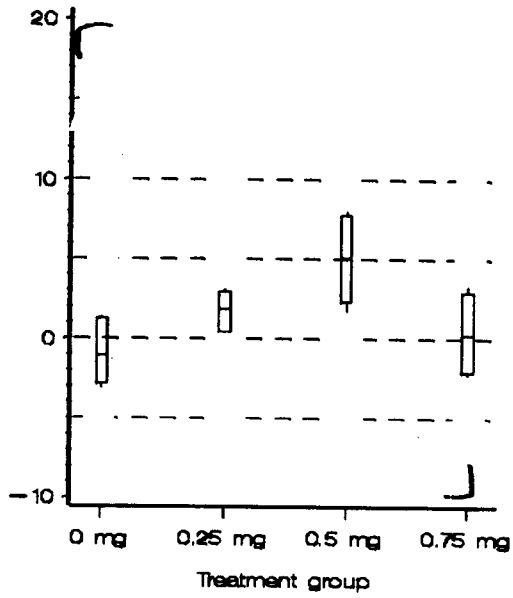

Figure 4
% change in lumbar spine BMD by race
Ethnic code= CAUC

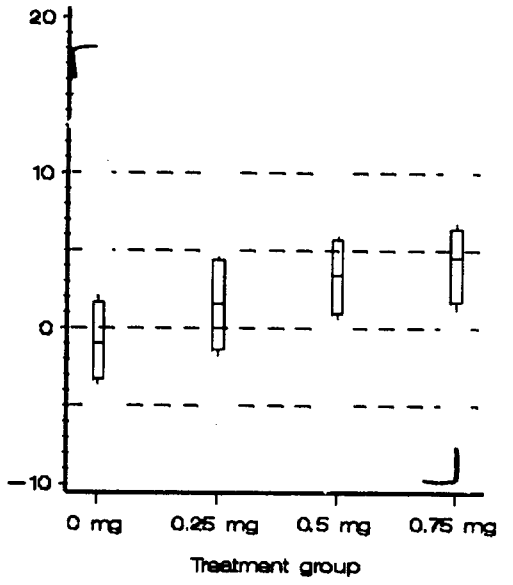

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Figure 4
% change in lumber spine BMD by race
Ethnic code=OTHER

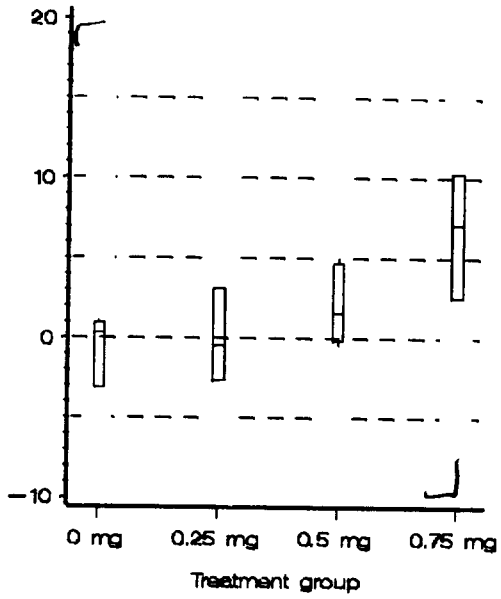

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Figure 5
% change in lumbar spine BMD by estrogen use
Estrogen use prior= N

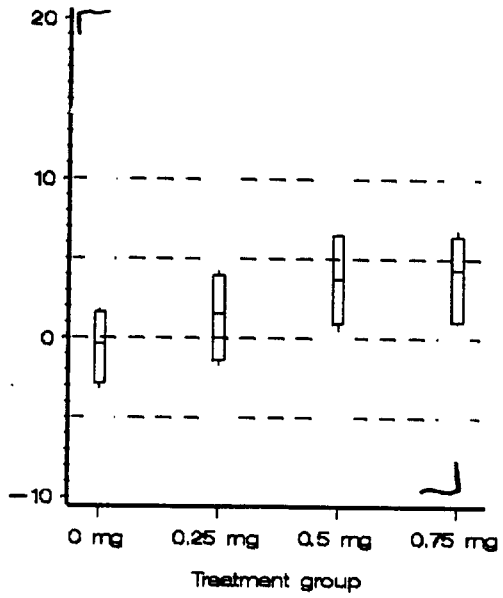

Figure 5
% change in lumbar spine BMD by estrogen use
Estrogen use prior= Y

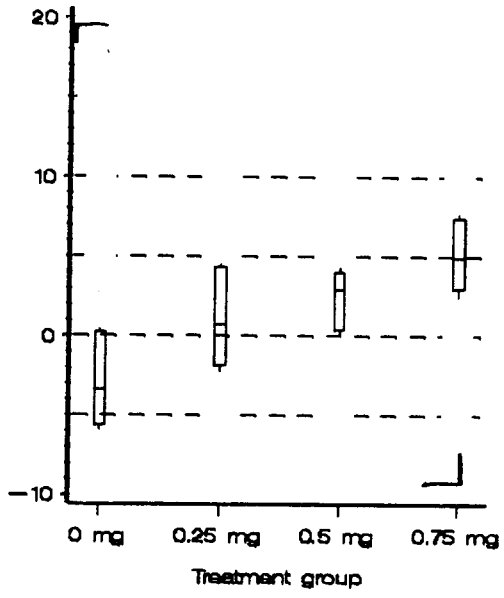

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Figure 6

% change in lumber spine BMD by yrs since hysterectomy

HYSTERCT= above median

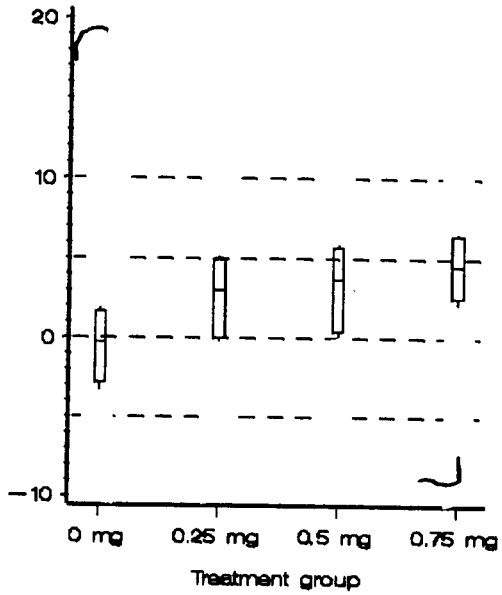

Figure 6

% change in lumber spine BMD by yrs since hysterectomy

HYSTERCT= below median

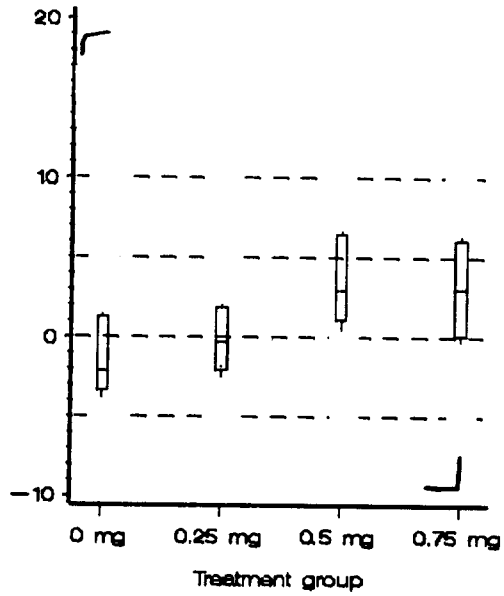

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Figure 7
% change in lumbar spine BMD by baseline t score
TSCORE= above median

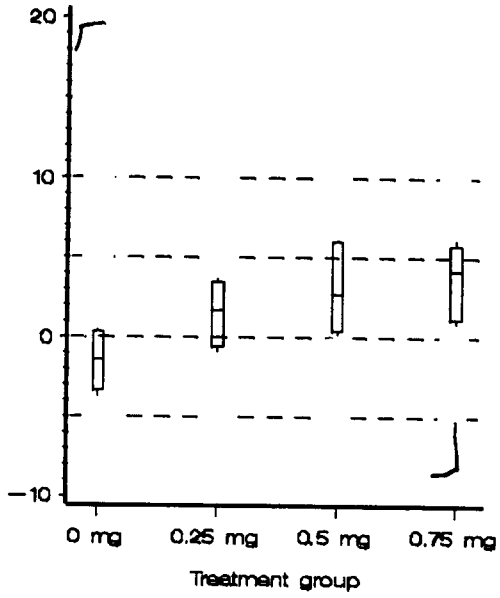

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Figure 7
% change in lumbar spine BMD by baseline t score
TSCORE= below median

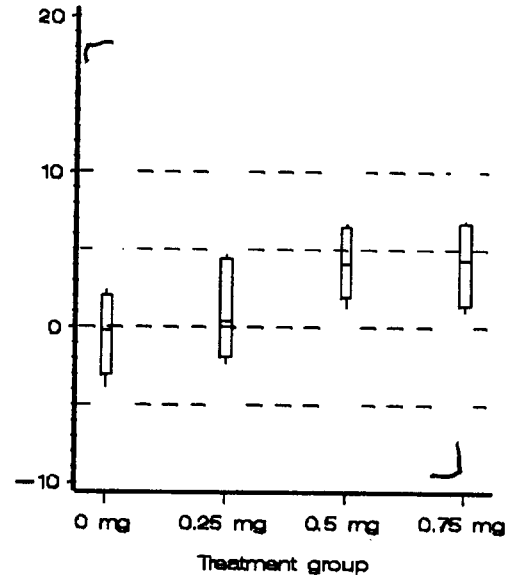

Figure 8
% change in lumbar spine BMD by BMI
BMI= above median

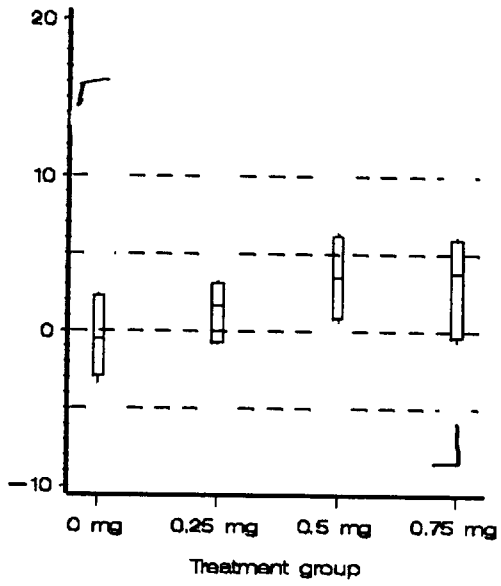

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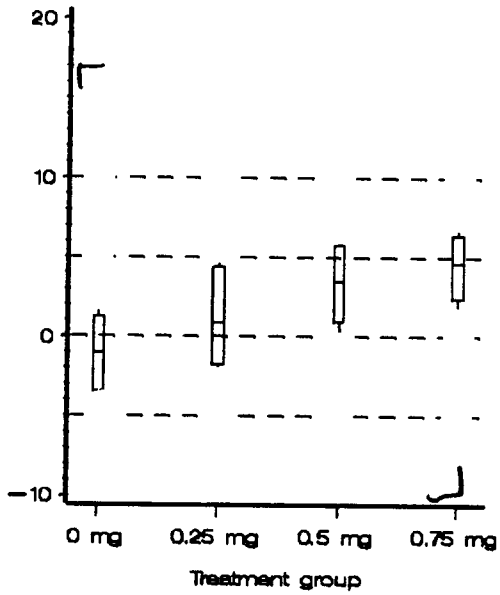
Figure 8
% change in lumbar spine BMD by BMI
BMI= below median



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/s/

Todd Sahlroot
10/24/01 12:12:31 PM
BIOMETRICS

S. Edward Nevius
11/2/01 10:08:36 AM
BIOMETRICS
Concur.

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-310

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-310 / N-000	Brand Name	Alora® TD system
OCPB Division (I, II, III)	DPE2	Generic Name	Estradiol transdermal system
Medical Division	DMEDP	Drug Class	
OCPB Reviewer	Robert Shore, Pharm.D.	Indication(s)	Prevention [redacted] of PMO.
OCPB Team Leader	Hae-Young Ahn, Ph.D.	Dosage Form	Transdermal system
		Dosing Regimen	0.025 mg/day applied twice weekly
Date of Submission	12-JAN-01	Route of Administration	topical
Estimated Due Date of OCPB Review	10-SEP-01	Sponsor	Watson Laboratories, Inc., Salt Lake City, Utah
PDUFA Due Date	16-NOV-01	Priority Classification	3S
Division Due Date	09-OCT-01		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE	[redacted]	[redacted]	[redacted]	[redacted]
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	[redacted]	[redacted]	
Tabular Listing of All Human Studies	X	[redacted]	[redacted]	
HPK Summary	X	[redacted]	[redacted]	
Labeling	X	[redacted]	[redacted]	
Reference Bioanalytical and Analytical Methods	X	[redacted]	[redacted]	[redacted] included
I. Clinical Pharmacology	[redacted]	[redacted]	[redacted]	[redacted]
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	[redacted]	[redacted]	[redacted]	[redacted]
Healthy Volunteers-	[redacted]	[redacted]	[redacted]	[redacted]
single dose:				
multiple dose:				
Patients-	[redacted]	[redacted]	[redacted]	[redacted]
single dose:				
multiple dose:	X	1		
Dose proportionality -	[redacted]	[redacted]	[redacted]	[redacted]
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	X	1		
Drug-drug interaction studies -	[redacted]	[redacted]	[redacted]	[redacted]
in-vivo effects on primary drug:				
in-vivo effects of primary drug:				

Dose stays in Appro

[redacted]

Analytic method. RIA

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In-vitro:				
Subpopulation studies -	[redacted]	[redacted]	[redacted]	[redacted]
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 2:				
Phase 3:				
PK/PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	1		
Population Analyses -	[redacted]	[redacted]	[redacted]	[redacted]
Data rich:				
Data sparse:				
II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:				
Relative bioavailability -	[redacted]	[redacted]	[redacted]	[redacted]
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]	1		

Alora® 0.05, 0.075, and 0.1 mg/day transdermal systems are approved under NDA 20-655 for: Treatment of moderate-to-severe vasomotor symptoms associated with the menopause; Treatment of vulval and vaginal atrophy, and; Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. NDA 21-310/N-000 seeks approval of Alora® 0.025 mg/day for the prevention [redacted] of postmenopausal osteoporosis.

One study has been submitted to section 6. Protocol 1996023 was a phase 3, 24 months' duration, dose-ranging clinical study in which PMO women were treated with either one of three Alora® TD systems or a placebo TD system. Pharmacokinetic samples for serum estradiol determination were obtained at baseline and after 12, 18, and 24 months of

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treatment. The pharmacokinetic analysis of this clinical study as well as an Emax model relating serum estradiol concentrations to absolute changes in bone mineral density have been submitted in Section 6.

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?	None at this time	
QBR questions (key issues to be considered)	• Is the lower strength 0.025mg/day system dose proportional to the higher approved strengths? • Are the pharmacokinetics and pharmacodynamic related?	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-310/N-000, HFD-850(Electronic Entry or Lee), HFD-510(Hedin), HFD-870(Ahnh, Malinowsky, Hunt), CDR.

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OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-310	Submission Date(s): 16-Jan-01
Brand Name	Alora®
Generic Name	Estradiol Transdermal Systems
Reviewer	Wei Qiu, Ph.D.
Team Leader	Hae-Young Ahn
OCPB Division	DPE II
ORM division	Metabolic and Endocrine Drug Products
Sponsor	Watson Laboratories, Inc., 417 Wakara Way, Salt Lake City, Utah 84108
Submission Type	Original NDA
Related NDA	NDA 20-655
Formulation; Strength(s)	Transdermal Patch; 0.025, 0.05, 0.075 and 0.1 mg/day
Indication	Prevention [redacted] of postmenopausal osteoporosis

I. Executive Summary

Watson Laboratories, Inc. submitted an NDA 21-310 for four strengths (surface areas) of Alora® Estradiol Transdermal System (EMTDS), 0.025 mg/day (9 cm^2), 0.05 mg/day (18 cm^2), 0.075 mg/day (27 cm^2), and 0.1 mg/day (36 cm^2) on 16-Jan-01.

Presently, three dosage strengths of Alora®, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day are marketed in accordance with NDA 20-655 that was approved by the Division of Reproductive and Urologic Drug Products for the treatment of moderate to severe vasomotor symptoms associated with menopause.

This application provided a clinical trial to support an additional indication of prevention [redacted] of postmenopausal osteoporosis for currently marketed dosage strengths of Alora®, as well as related information to support a new 0.025 mg/day dosage strength for the osteoporosis indication. The new low dosage strength has an identical formulation to the currently approved strengths and differs only with respect to its surface area.

A. Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-310 submitted on 16-Jan-01. The overall Human Pharmacokinetic Section is acceptable to OCPB. Labeling comments outlined in the labeling section of the review should be conveyed to the sponsor as appropriate.

Wei Qiu, Ph.D.
Division of Pharmaceutical Evaluation II

Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader

FT initialed by Hae-Young Ahn, Ph.D., Team Leader

DFS CODE: AP

II. Table of Contents

III. Summary of CPB Findings

Dose proportionality of the 0.025 mg/day, 0.05 mg/day and 0.075 mg/day strengths was assessed by measuring serum estradiol concentrations in the study population participating in a placebo-controlled safety and efficacy study in osteoporosis (Protocol 1996023). Serum samples were collected at a pre-treatment and at the end of 12 months (Cycle 13), 18 months (Cycle 20), and 24 months (Cycle 26) of treatment and analyzed for estradiol using

The mean (SD) uncorrected and baseline-corrected steady-state serum estradiol concentrations, average for Cycles 13, 20, and 26, are provided in **Table 1**.

Table 1. Steady-State Serum Estradiol Concentrations (pg/ml) for the Placebo and Alora® Treatments

Treatment	Uncorrected	**Baseline-Corrected**
Placebo	9.3 (8.80)	3.2 (8.62)
Alora 0.025 mg/day	24.5 (12.35)	18.6 (12.17)
Alora 0.05 mg/day	42.6 (23.67)	35.9 (23.78)
Alora 0.075 mg/day	56.7 (36.78)	50.1 (36.07)

Dose proportionality was evaluated using the weighted regression approach. The results of the weighted regression analysis indicated that the average baseline-corrected steady-state serum estradiol concentrations were proportional for systems with delivery rates of 0.025 to 0.075 mg/day.

The relationship between serum estradiol concentrations and the changes in bone mineral

density at 1 and 2 years was investigated using an Emax model. The mean (SD) % changes in bone mineral density at 1 and 2 years during treatment with placebo and the 3 strengths of Alora® are provided in **Table 2.**

Table 2. Mean (SD) % Changes in Bone Mineral Density at 1 and 2 years during Treatments with Placebo and Alora Systems

Treatment	1 Year	2 Year
Placebo	-0.06 (0.50)	-0.59 (0.53)
Alora 0.025 mg/day	1.43 (0.42)	1.65 (0.59)
Alora 0.05 mg/day	3.52 (0.53)	4.08 (0.47)
Alora 0.075 mg/day	4.34 (0.46)	4.82 (0.61)

These data indicated an overall relationship between increased bone mineral density at 1 and 2 years and increasing dose regarding to the mean values. However, the model that was fitted to the individual data at 2 years had low coefficients ($r^2 = 0.486$) of determination indicating a lack of correlation between change in bone mineral density and estradiol concentrations. (**Figure 1**).

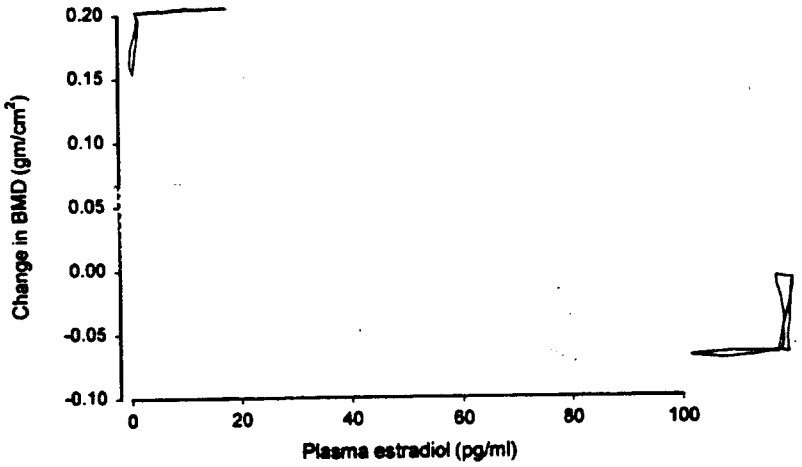

Figure 1. Agreement between the Observed Data and the Fitted Emax Function for Changes in Bone Mineral Density Data

IV. QBR

A. General Clinical Pharmacology

Q. What is the basis for selecting BMD as a biomarker?

Osteoporosis is a metabolic bone disease that affects mainly the elderly. Estrogen deficiency resulting from menopause leads to an earlier onset of the disease in women compared to men. Particularly striking is the rapid decline in bone mineral density (BMD) seen in predominantly

cancellous bone found in the vertebrae. The progressive loss of bone mass eventually leads to fracture that is the clinical endpoint for osteoporosis.

Q. What is the dose-concentration relationship?

Previously, the dose proportionality of the strengths 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (E94004) was assessed. It was pointed out previously (NDA 20-655 review) that strict dose proportionality between the three systems was not observed due to the large variability in estradiol pharmacokinetics and baseline (endogenous) estradiol.
In this application, dose proportionality of the strengths 0.025 mg/day, 0.05 mg/day and 0.075 mg/day was evaluated in a Phase III clinical trial (Protocol 1996023). Study 1996023 was a double-blind, double-dummy, randomized, placebo-controlled, parallel, multi-center, dose-ranging study of 24 months' duration in postmenopausal women. Patients were assigned to one of the following 4 treatment groups according to a previously established randomization code: (1) Estradiol 0.025 mg/day (9 cm^2 system) and placebo (18 cm^2 system); (2) 0.05 mg/day (18 cm^2 system) and placebo (9 cm^2 system); (3) 0.075 mg/day (18 cm^2 and 9 cm^2 active systems); or (4) placebo (18 cm^2 and 9 cm^2 placebo system). Each system was worn for about 3.5 days. Each 28-day treatment was referred to as a cycle. Each patient was to undergo 26 consecutive cycles during this 2-year study.

Serum was harvested from blood samples collected prior to the start of treatment, and after 12, 18, and 24 months of treatment. These assessment times corresponded to the end of Cycles 13, 20, and 26, respectively. Blood samples were collected at any time within the 3.5-day interval. The time of blood collection and the date and time of application of the last system were recorded to permit calculation of the interval between system application and blood sampling. Serum samples were analyzed for estradiol using _____

analytical method

A total of 355 patients were enrolled into this study. Data from 34 of the patients were excluded from the analysis because one or both systems were not adhered at the time of blood sampling, the interval between system application and blood sampling exceeded 100 hour, or the patients were taking additional forms of estrogen replacement therapy at the time of blood sampling. A total of 321 patients had serum estradiol concentration data at baseline.

Statistical comparison of the baseline-adjusted serum estradiol concentrations on the first, second, third and fourth day of application did not identify any significant differences ($p>0.05$) between application days for any of the treatment groups. The differences in paired baseline adjusted serum estradiol concentrations at Cycle 13 and Cycle 20, and Cycle 13 and Cycle 26 were not statistically significant ($p>0.05$) for any of the treatment groups. The steady-state was attained by Cycle 13 and sustained to Cycle 26 for baseline-adjusted estradiol concentrations. The mean (SD) serum estradiol concentrations for the placebo and 3 Alora treatments in the prevention of osteoporosis trial are given in **Table 4**. The numbers of patients who contributed to the mean calculations are shown as well.

Table 4. Mean (SD) Serum Estradiol Concentrations at Baseline and During Treatments with Placebo and Alora Systems

Time	Descriptive Statistic	Placebo	Alora 0.025 mg/day	Alora 0.050 mg/day	Alora 0.075 mg/day
Baseline	Mean (SD)	6.3 (2.82)	6.4 (3.10)	6.7 (3.73)	6.6 (3.62)
	Number of Patients	79	81	78	83
Cycle 13	Mean (SD)	8.7 (6.98)	25.0 (11.49)	40.5 (22.58)	54.9 (32.74)
	Number of Patients	59	45	47	46
Cycle 20	Mean (SD)	8.2 (3.45)	24.6 (11.64)	42.5 (19.84)	61.9 (33.92)
	Number of Patients	50	41	44	40
Cycle 26	Mean (SD)	10.9 (12.71)	23.8 (14.23)	45.0 (28.11)	53.8 (42.94)
	Number of Patients	58	38	45	45

According to the sponsor, a test for overall dose proportionality of average, baseline-adjusted, steady-state serum concentrations for each individual patient was performed using the weighted regression approach. The quadratic term, c, in the following equation was tested to determine if it differed significantly from zero:

$Y = a + b(dose) + c(dose^2)$

where Y was the mean estradiol concentration at steady state (Cycles 13, 20, and 26) for each individual patient. Similarly, the intercept term, a, in the following equation also was tested to determine if it differed significantly from zero:

$Y = a + b(dose)$

The results of the statistical analysis of the average baseline-adjusted steady-state serum concentration data are summarized in **Table 5.**

Table 5. Weighted Regression Analysis of the Dose Proportionality Data in the Evaluable Population

Test	Variable	Parameter Estimate	SE	P-value	Conclusion
Step 1: Test for Linearity	a	1.32	11.06	0.9049	Linearity Achieved
	b	0.65	0.54	0.2300	
	c	0.00	0.01	**0.9943**	
Step 2: Test for Dose Proportionality	a	1.40	3.54	**0.6934**	Dose Proportionality Achieved
	b	0.65	0.08	0.0001	

The results showed that both the coefficient of the quadratic term, c, and the intercept term, a, were not significantly different from zero ($p>0.05$), indicating that serum estradiol concentrations were dose proportional for systems with delivery rates of 0.025 to 0.075 mg/day.

Q. What are the characteristics of the exposure-response relationships for efficacy?

The decline in endogenous estradiol production that occurs at menopause leads to an accelerated loss in bone mineral density and to the development of postmenopausal osteoporosis. The relationship between the average, baseline-adjusted, steady-state serum concentration (C) and absolute changes in bone mineral density (R) was investigated using the Emax model.

$R = Emax \cdot C/(C_E50 + C) + PR$

Where Emax was the maximum response achieved, C_E50 was the serum concentration producing 50% of the maximum effect, and PR is the placebo response. The placebo response, PR, was set as a fixed variable equal to the average change in bone mineral density for the placebo group only (PR = -0.0053).

The mean (SD) % changes in bone mineral density at 1 and 2 years during treatment with placebo and the 3 strengths of Alora are provided in **Table 2.** These data indicate a dose-response relationship in the mean data at 1 and 2 years. Non-linear regression results for the Emax model are given in **Table 6.**

Table 6. Non-Linear Regression Results of Emax Model (Evaluable Population)

Dependent Variable	Parameter	Estimate	SE	95% CI	p-value	Model R^2
Change in Bone Mineral Density (g/cm^2)[a]	Emax	0.0610	0.0122	(0.0368, 0.0852)	< .001	**0.49**
	C_E50	11.9063	8.5573	(-5.0235, 28.8361)		

[a]. Note that SE and 95% CI were based on asymptotic variances from non-linear regression approach.

The model that was fitted to the individual data at 2 years had low coefficients of determination indicating a lack of correlation between change in bone mineral density and doses.

B. General Biopharmaceutics

Q. Are the 0.025 mg/day strength batches used in the clinical trial bioequivalent to the to-be-marketed products?

The comparison between the 0.025 mg/day strength batches used in the osteoporosis study (Protocol no. 1996023) and to-be-marketed products is given in Table 3. The [redacted] were used in clinical trial batches (96Z163 and 97Z184) and to-be-marketed products, respectively. The Alora

[redacted]

Table 3. Comparison between System used in Phase III Osteoporosis Clinical Study No. 1996023 and To-Be-Marketed Products

Component	Solution Percent by Weight		Note
	Target (%)	Range (%)	
Estradiol, USP	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	Clinical Trial Batches (96Z163 and 97Z184) used [redacted] To-Be-Marketed Products used [redacted]
Sorbitan MonoOleate, NF	[redacted]	[redacted]	
Total	[redacted]		

The 0.025 mg/day strength used in the clinical trial are considered to be bioequivalent to those to-be-marketed products based on two reasons although a formal BE trial has not been conducted.

First, the drug substance, components, and quantitative composition of the estradiol transdermal system, 0.025 mg/day strength, are identical to the currently approved dosage strengths with the exception of the system size.
Secondly, it has been shown that the 0.05 mg/day strength manufactured with the [redacted] (clinical) and [redacted] (to-be-marketed) versions of the [redacted] were bioequivalent

Trade Secret

APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Watson Laboratories, Inc.	October 19, 2001
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
(801) 588-6200	(801) 583-8135
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 417 Wakara Way, Salt Lake City, Utah 84108	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-310

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Estradiol Transdermal System (EMTDS)	Alora® Estradiol Transdermal System

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Estra-1,3,5 (10)-triene-3, 17-diol	None

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Transdermal System	0.025, 0.05, 0.075 and 0.1 mg/day	Transdermal

(PROPOSED) INDICATION(S) FOR USE: Treatment of moderate-to-severe vasomotor symptoms associated with menopause. Treatment of vulval and vaginal atrophy. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. Prevention of postmenopausal osteoporosis.

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☒ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Response to Request for Information

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See Attached

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA #20-655 Alora

This application contains the following items: *(Check all that apply)*

☐	1. Index	
☐	2. Labeling *(check one)*	☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50(c))	
☒	4. Chemistry section	
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)	
☐	B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)	
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)	
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)	
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))	
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)	
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)	
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☐	12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)	
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))	
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A)	
☐	15. Establishment description (21 CFR Part 600, if applicable)	
☐	16. Debarment certification (FD&C Act 306(k)(1))	
☐	17. Field copy certification (21 CFR 314.50(k)(3))	
☐	18. User Fee Cover Sheet (Form FDA 3397)	
☐	19. Financial Information (21 CFR Part 54)	
☐	20. OTHER *(Specify)*	

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Dorothy A. Frank	Dorothy A. Frank, M.S., R.A.C. Executive Director, Regulatory Affairs	October 19, 2001
ADDRESS *(Street, City, State, and ZIP Code)* 417 Wakara Way Salt Lake City, Utah, 84108		TELEPHONE NUMBER (801) 588-6200

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

WATSON Laboratories, Inc.

DUPLICATE

A Subsidiary of Watson Pharmaceuticals, Inc. N-000-BL

May 11, 2001

John K. Jenkins, M.D., Director
Division of Metabolic and Endocrine
Drug Products (HFD- 510)
CDER, Document Room 14-B-19
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-310 Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day
Revised labeling

Dear Dr. Jenkins:

Reference is made to the telephone conversation on May 2, 2001 between Randy Hedin from DMEDP and Dorothy Frank from Watson Laboratories, Inc. During this conversation, Mr. Hedin requested an electronic copy of the labeling in Microsoft Word and requested that Watson amend the labeling to include only the changes related to the osteoporosis indication. Mr. Hedin said that the additional changes made to the label unrelated to the osteoporosis indication could not be reviewed by DMEDP, and that they should be submitted to DRUDP for consideration. As requested enclosed with this submission are the following items:

- Amended Package Insert
- Annotated Package Insert showing the changes from the current commercial label
- Amended Patient Information Leaflet
- Annotated Patient Information Leaflet showing the changes from the current commercial label
- CD-ROM containing electronic copies of the labeling

If you have any questions or need any additional information, please feel free to contact me by telephone at (801) 588-6200 or by fax at (801) 583-8135.

Sincerely,

Dorothy A. Frank

Dorothy A. Frank, M.S., R.A.C.
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Research Park, 417 Wakara Way, Salt Lake City, UT 84108 • Tel: 801/588-6200 • Fax: 801/583-6042

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

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Watson Laboratories, Inc.	May 11, 2001
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
(801) 588-6200	(801) 583-8135
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
417 Wakara Way Salt Lake City, Utah 84108	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-310

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CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
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IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION To provide revised draft labeling

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NDA #20-655 Alora

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5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
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Dorothy A. Frank	Dorothy A. Frank, M.S., R.A.C. Director, Regulatory Affairs	May 11, 2001

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
417 Wakara Way Salt Lake City, Utah, 84108	(801) 588-6200

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CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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DUPLICATE

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

May 11, 2001

N 000 SU
ORIG AMENDMENT

John K Jenkins, M.D., Director
Division of Metabolic and
Endocrine Drug Products, HFD 510
Center for Drug Evaluation and Research
Document Room 14B-10
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: **NDA #21-310**: Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day
Amendment – 120 day safety report

Dear Dr. Jenkins:

In accordance with 21 CFR 314.50(d)(5)(vi)(b) and section 505(i) of the act, Watson Laboratories, Inc. is submitting this correspondence to fulfill the requirement for submission of a 120-day Safety Update for **NDA #21-310.**

There is no new safety information regarding this product.

If you have any questions or comments regarding the information provided, please do not hesitate to contact me by phone (801) 588-6200 or fax (801) 583-8135.

Sincerely,

Dorothy A. Frank, M.S., R.A.C.
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Research Park, 417 Wakara Way, Salt Lake City, UT 84108 • Tel: 801/588-6200 • Fax: 801/583-6042

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Watson Laboratories, Inc.	May 11, 2001
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
(801) 588-6200	(801) 583-8135
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
417 Wakara Way Salt Lake City, Utah 84108	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-310

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Estradiol Transdermal System (EMTDS)	Alora® Estradiol Transdermal System

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* Estra-1,3,5 (10)-triene-3, 17-diol

CODE NAME *(If any)* None

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Transdermal System	0.025, 0.05, 0.075 and 0.1 mg/day	Transdermal

(PROPOSED) INDICATION(S) FOR USE: Treatment of moderate-to-severe vasomotor symptoms associated with menopause. Treatment of vulval and vaginal atrophy. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. Prevention of postmenopausal osteoporosis.

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION 120 day safety report

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA #20-655 Alora

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50(c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A)
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306(k)(1))
☐	17. Field copy certification (21 CFR 314.50(k)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* 120 day safety report

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Cheri L. Peterson for D. Frank	Dorothy A. Frank, M.S., R.A.C. Director, Regulatory Affairs	May 11, 2001

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
417 Wakara Way Salt Lake City, Utah, 84108	(801) 588-6200

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

)artment of Health and Human Services
)d and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

ORIGINAL

WATSON
Laboratories, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

February 14, 2000

John K. Jenkins, M.D., Director
Division of Metabolic and Endocrine
Drug Products (HFD- 510)
CDER, Document Room 14-B-19
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-310 Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day

Dear Dr. Jenkins:

In accordance with the Federal Food, Drug, and Cosmetic Act, Watson Laboratories, Inc. is submitting an amendment to our New Drug Application for a new system size and indication for Alora Estradiol Transdermal Systems. Alora is also subject of our NDA —— that was reviewed and approved by the Division of Reproductive and Urologic Drug Products. Three dosage strengths, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day are approved in NDA —— for the treatment of moderate to severe vasomotor symptoms associated with menopause.

This amendment is submitted to withdraw the words ———— from the indication proposed in our original submission for 0.025 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day Alora Estradiol Transdermal Systems. The new proposed indication is "prevention of postmenopausal osteoporosis".

If you have any questions or need any additional information, please feel free to contact me by telephone at (801) 588-6200 or by fax at (801) 583-8135.

Sincerely,

Dorothy A. Frank, M.S., R.A.C.
Director, Regulatory Affairs

Desk copy: Randy Hedin

REVIEWS COMPLETED | S
CSO ACTION
LETTER | N.A.I. | MEMO
CSO INITIALS | DATE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Watson Laboratories, Inc.	February 14, 2003
TELEPHONE NO. (Include Area Code) (801) 588-6200	FACSIMILE (FAX) Number (Include Area Code) (801) 583-8135
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 417 Wakara Way Salt Lake City, Utah 84108	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)*

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Estradiol Transdermal System (EMTDS)	Alora® Estradiol Transdermal System

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* Estra-1,3,5(10)-triene-3,17-diol — CODE NAME *(If any)* None

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Transdermal System	0.025, 0.05, 0.075 and 0.1 mg/day	Transdermal

(PROPOSED) INDICATION(S) FOR USE: Treatment of moderate-to-severe vasomotor symptoms associated with menopause. Treatment of vulval and vaginal atrophy. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. Prevention of postmenopausal osteoporosis.

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION To revise indication

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
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See attached

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA #20-555 Alora

This application contains the following items: *(Check all that apply)*

- ☐ 1. Index
- ☐ 2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
- ☐ 3. Summary (21 CFR 314.50(c))
- ☐ 4. Chemistry section
  - ☐ A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
  - ☐ B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
  - ☐ C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- ☐ 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- ☐ 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- ☐ 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- ☐ 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- ☐ 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- ☐ 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
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- ☐ 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- ☐ 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- ☐ 14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A)
- ☐ 15. Establishment description (21 CFR Part 600, if applicable)
- ☐ 16. Debarment certification (FD&C Act 306(k)(1))
- ☐ 17. Field copy certification (21 CFR 314.50(k)(3))
- ☐ 18. User Fee Cover Sheet (Form FDA 3397)
- ☐ 19. Financial Information (21 CFR Part 54)
- ☒ 20. OTHER *(Specify)* Te revise indication

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211or applicable regulations. Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Dorothy A. Frank for D. Frank	Dorothy A. Frank, M.S., R.A.C. Director, Regulatory Affairs	[illegible]

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
417 Wakara Way Salt Lake City, Utah 84108	[illegible]

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Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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WITHHOLD 119 PAGE (S)

Draft

Labeling

MEMORANDUM

Re: NDA 21-310, Alora Estradiol Transdermal System, Final Labeling

Date: April 4, 2002

Referenced Document: Response to Approvable Letter, February 5, 2002, N000 AL.

Medical Officer: Patricia R. Beaston-Wimmer, M.D., Ph.D.

Medical Team Leader: Eric Colman, M.D.

The revised proposed label has been reviewed in full. Watson has incorporated the suggestions from this Medical Reviewer into the osteoporosis section. The changes made in reference to the indication for postmenopausal osteoporosis are acceptable.

The remainder of the label has been negotiated with the Division of Urologic and Reproductive Drug Products (HFD-580).

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

/s/

Patricia Beaston-Wimmer
4/4/02 02:25:46 PM
MEDICAL OFFICER

Eric Colman
4/8/02 08:34:37 AM
MEDICAL OFFICER

DUPLICATE

WATSON
Laboratories, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

16 October, 2001

Division of Metabolic and Endocrine Drug Products (HFD- 510)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Document Room 14-B-19
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMEN

RE: NDA 21-310, Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day

In response to telephone inquiries on October 1 and 4 of this year by Dr. Wei Qiu regarding the biopharmaceutical review of NDA 21-310, we are providing the following clarifying information, and amending the proposed labeling. The details are provided below.

A. Dr. Qiu requested clarification regarding the calculations in Table 4 (page 27 in volume 6.01 of the NDA). In response to that question, we are providing herewith an amended copy of Table 4 (the values have not changed, but a typographical error was corrected in Step 1: the description of variable "c" was "Dose", when it should have been "Dose^2". Dr. Qiu also inquired about the value of 0.65 reported for "Dose" (slope) shown in Step 2; we are providing the following explanation for that value:

   In the analysis of the dose proportionality data we did not attach any significance to the numerical value of the slope but simply tested to see if the coefficient of the quadratic term in the quadratic equation and the intercept in the linear equation were significantly different from zero. In Table 4 the dose (or more accurately the daily rate) was expressed in μg/day hence the value of 0.65 but the units in this case do not make a great deal of sense (i.e. $pg \cdot ml^{-1} \cdot \mu g^{-1} \cdot day$). Using the same mass units, the slope value (which essentially represents 1/clearance) would be 6.5×10^{-7} $ml^{-1} \cdot day$. The clearance value calculated from the slope is 64.1 L/hr which is in close agreement with the values estimated from other studies (see: Draft Labeling, Table 1).

B. Dr. Qiu inquired regarding the source of the data, in Table 2 of the proposed insert, labeled as "Study 1" and "Study 2". Watson's response follows:

   Studies 1 and 2 in Table 2 refer to Protocols E94001 and E94002, respectively, that were included in the original NDA for Alora in the treatment of menopausal symptoms (NDA 20-655). The values reported for the two studies were derived from the individual serum level data listed in the Pharmacokinetic Section of NDA 20-655 in Volume XXV (Study 1; Protocol E94001; Appendix C) and Volume XXVI (Study 2: Protocol E94002; Appendix C). With the addition of the new strength of Alora it was believed that this data presented in a tabular format would add clarity to the

pharmacokinetics and delivery of estradiol from the different available dosage strengths.

C. The proposed insert contains, directly under Figure 3, the statement,

[ ]

Ms. Qiu requested clarification of the source of the number

The number — was incorrectly transcribed from an earlier draft report for evaluable subjects, and has now been corrected to — subjects. This number represents the number of evaluable patients in the study.

After careful consideration we would propose the following change to the draft labeling, to more clearly and accurately represent the data referring to dose proportionality (under Figure 3):

[ ]

We trust this provides sufficient clarification of Dr. Qiu's questions to permit continued review of this NDA. If you have any questions or need any additional information, please feel free to contact me by telephone at (801) 588-6200 or by fax at (801) 583-8135.

Best Regards,

Dorothy A. Frank

Dorothy A. Frank, M.S., R.A.C.
Executive Director, Proprietary Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Watson Laboratories, Inc.	DATE OF SUBMISSION October 16, 2001
TELEPHONE NO. (Include Area Code) (801) 588-6200	FACSIMILE (FAX) Number (Include Area Code) (801) 583-8135
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 417 Wakara Way Salt Lake City, Utah 84108	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-310

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* Estradiol Transdermal System (EMTDS)

PROPRIETARY NAME *(trade name)* IF ANY Alora® Estradiol Transdermal System

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* Estra-1,3,5 (10)-triene-3, 17-diol

CODE NAME *(If any)* None

DOSAGE FORM: Transdermal System

STRENGTHS: 0.025, 0.05, 0.075 and 0.1 mg/day

ROUTE OF ADMINISTRATION: Transdermal

(PROPOSED) INDICATION(S) FOR USE: Treatment of moderate-to-severe vasomotor symptoms associated with menopause. Treatment of vulval and vaginal atrophy. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. Prevention of postmenopausal osteoporosis.

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Response to Request for Information

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See Attached

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA #20-655 Alora

with respect to the rate and extent of estradiol delivery after single application of the respective systems to the lower abdomen of healthy postmenopausal women. The sponsor received approval to use [redacted] in April 1998 (supplemental filing NDA 20-655/S-002).

Analytical
All
Redacted
- OJT

C. Analytical

Q. What was the bioanalytical method used to assess serum estradiol concentrations? Has the assay method adequately validated?

[redacted]

V. Labeling

(~~Strikeout text~~ should be removed from labeling; Double <u>underlined text</u> should be added to labeling; ☞ indicates an explanation only and is not intended to be included in the labeling)

Pharmacokinetics

[redacted]

WITHHOLD 11 PAGE (S)

Draft

Labeling

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

/s/

Wei Qiu
1/16/02 11:31:09 AM
PHARMACOLOGIST

Hae-Young Ahn
1/16/02 11:50:48 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-310

ADMINISTRATIVE DOCUMENTS

~~CORRESPONDENCE~~

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-310 /SE_____ - _____

Drug Alora (estradiol transdermal system) Applicant Watson Laboratories

RPM Samuel Wu Phone 301-827-6416

☒ 505(b)(1)
☐ 505(b)(2) Reference listed drug _____

☐ Fast Track ☐ Rolling Review Review priority: ☒ S ☐ P

Pivotal IND(s) _____

Application classifications:
Chem Class 3 (new formulation)
Other (e.g., orphan, OTC) _____

PDUFA Goal Dates:
Primary Nov 16, 2001
Secondary Jan 16, 2002

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ☒ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption

- Action Letter..... ☒ AP ☐ AE ☐ NA

- Labeling & Labels
  FDA revised labeling and reviews..... X
  Original proposed labeling (package insert, patient package insert) X
  Other labeling in class (most recent 3) or class labeling..... X
  Has DDMAC reviewed the labeling? Will be in DFS..... ☐ Yes (include review) ☐ No
  Immediate container and carton labels Ar on Tue (4/13)..... _____
  Nomenclature review ..... _____

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ☒ is not on the AIP.
  Exception for review (Center Director's memo)..... _____
  OC Clearance for approval..... _____

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ☒ Materials requested in AP letter
- Post-marketing Commitments — N/A
  - Agency request for Phase 4 Commitments.....
  - Copy of Applicant's commitments .....
- Was Press Office notified of action (for approval action only)? ☐ Yes ☒ No
  - Copy of Press Release or Talk Paper.....
- Patent
  - Information [505(b)(1)] X
  - Patent Certification [505(b)(2)].....
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....
- Exclusivity Summary X
- Debarment Statement X
- Financial Disclosure
  - No disclosable information X
  - Disclosable information – indicate where review is located page 9 of clinical review X
- Correspondence/Memoranda/Faxes X
- Minutes of Meetings .....
  - Date of EOP2 Meeting _____
  - Date of pre NDA Meeting _____
  - Date of pre-AP Safety Conference N/A
- Advisory Committee Meeting ..... N/A
  - Date of Meeting .....
  - Questions considered by the committee .....
  - Minutes or 48-hour alert or pertinent section of transcript .....
- Federal Register Notices, DESI documents ..... N/A

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) X
- Clinical review(s) and memoranda X
- Safety Update review(s) ..... N/A
- Pediatric Information

☒ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
Pediatric Page 23 of the Summary Volume 1.0.1 X
☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☒ Not Applicable

- Statistical review(s) and memoranda X
- Biopharmaceutical review(s) and memoranda X
- Abuse Liability review(s) ..... N/A
  Recommendation for scheduling .....
- Microbiology (efficacy) review(s) and memoranda ..... N/A
- DSI Audits (see filing minutes) ..... N/A
  ☐Clinical studies ☐ bioequivalence studies .....

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- CMC review(s) and memoranda X
- Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A
- DMF review(s) (see CMC reviews) ..... N/A
- Environmental Assessment review/FONSI/Categorical exemption X
- Micro (validation of sterilization) review(s) and memoranda ..... N/A
- Facilities Inspection (include EES report)
  Date completed 3/8, 3/16, 3/20 2001 ..... ☒ Acceptable ☐ Not Acceptable
- Methods Validation (satisfactory, page 21 of CMC Review) ☒ Completed ☐ Not Completed

---

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Pharm/Tox review(s) and memoranda X
- Memo from DSI regarding GLP inspection (if any) ..... N/A
- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report ..... N/A

The application consists of a total of 38 volumes, each numbered sequentially starting with volume 1.1 and ending with volume 1.38. Information contained in the NDA is identified in the index of the application with an item number, item title, and the corresponding location by NDA volume number. Each item of the NDA has been independently numbered by item volume and page number. Each page of the application includes the section volume number and section page number at the center of the bottom of the page.

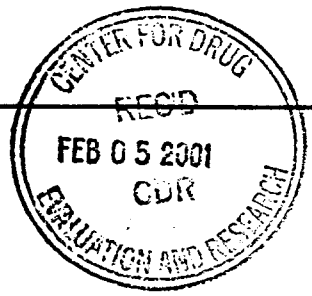
If you have any questions or need any additional information, please feel free to contact me by telephone at (801) 588-6200 or by fax at (801) 583-8135.

Sincerely,

Dorothy A. Frank

Dorothy A. Frank, M.S., R.A.C.
Director, Regulatory Affairs

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.



January 12, 2001

John K. Jenkins, M.D., Director
Division of Metabolic and Endocrine
Drug Products (HFD- 510)
CDER, Document Room 14-B-19
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-310 Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day

Dear Dr. Jenkins:

In accordance with the Federal Food, Drug, and Cosmetic Act, Watson Laboratories, Inc. is submitting a New Drug Application for Alora Estradiol Transdermal Systems (also referred to as EMTDS in this application).

This application provides clinical data to support an additional indication of "prevention —— of postmenopausal osteoporosis" for currently marketed dosage forms of Alora, as well as Chemistry, Manufacturing, and Controls information and clinical data to support a new 0.025 mg/day dosage strength for the osteoporosis indication.

Three dosage strengths of Alora, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day are currently marketed in accordance with our NDA #20-655 that was approved by the Division of Reproductive and Urologic Drug Products (DRUDP) for the treatment of moderate to severe vasomotor symptoms associated with menopause. Regulations and FDA guidance provide for submission of information contained in this new NDA as a supplement to our approved NDA #20-655. However, FDA has requested submission of a new NDA for their administrative convenience because responsibility for review of information supporting the new indication is not assigned to DRUDP, but to the Division of Metabolic and Endocrine Drug Products.

Mike Jones of the Office of the Center Director also advised us in a teleconference on September 6, 2000 that half of the full user fee amount is required for this submission, as that is the fee that would be required for submission of a supplemental application with clinical data.

This application is being submitted in a combination of paper and electronic files. Complete paper copies of the archival and review copies are provided except for Sections 2, 11, and 12. Section 2 contains Labeling, and is provided in both paper and electronic files. The electronic copy of Section 2 is provided on 1 CDROM at an approximate size of 1 megabyte. Section 11 contains Case Report Tabulations and is provided in the archival copy only, on 1 CDROM at an approximate size of 30 megabytes. Section 12 contains Case Report Forms for Serious Adverse Events and Dropouts Due to Adverse Events and is provided in the archival copy only, on 1 CDROM at an approximate size of 242 megabytes. The software used to check these files for viruses was Norton Antivirus ——

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Watson Laboratories, Inc.	Januay 12, 2001
TELEPHONE NO. (Include Area Code) (801) 588-6200	**FACSIMILE (FAX) Number (Include Area Code)** (801) 583-8135
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 417 Wakara Way Salt Lake City, Utah 84108	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-310

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Estradiol Transdermal System (EMTDS)	Alora® Estradiol Transdermal System

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* Estra-1,3,5 (10)-triene-3, 17-diol — CODE NAME *(If any)* None

DOSAGE FORM: Transdermal System — STRENGTHS: 0.025, 0.05, 0.075 and 0.1 mg/day — ROUTE OF ADMINISTRATION: Transdermal

(PROPOSED) INDICATION(S) FOR USE: Treatment of moderate-to-severe vasomotor symptoms associated with menopause. Treatment of vulval and vaginal atrophy. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. Prevention of postmenopausal osteoporosis.

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☒ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Add new indication and dosage strength.

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

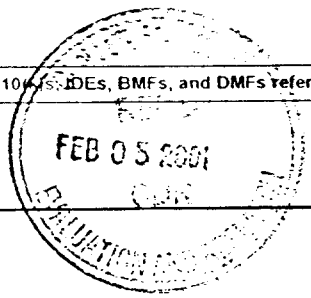
NUMBER OF VOLUMES SUBMITTED 38 — THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA #20-655 Alora



This application contains the following items: *(Check all that apply)*

☒	1. Index	
☒	2. Labeling *(check one)*	☒ Draft Labeling ☐ Final Printed Labeling
☒	3. Summary (21 CFR 314.50(c))	
☒	4. Chemistry section	
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)	
☐	B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
☒	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)	
☒	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)	
☒	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)	
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))	
☒	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)	
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)	
☒	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)	
☒	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)	
☒	12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)	
☒	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))	
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A)	
☐	15. Establishment description (21 CFR Part 600, if applicable)	
☒	16. Debarment certification (FD&C Act 306(k)(1))	
☒	17. Field copy certification (21 CFR 314.50(k)(3))	
☒	18. User Fee Cover Sheet (Form FDA 3397)	
☒	19. Financial Information (21 CFR Part 54)	
☐	20. OTHER *(Specify)*	

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Dorothy A. Frank	Dorothy A. Frank, M.S., R.A.C. Director, Regulatory Affairs	01/12/01

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
417 Wakara Way Salt Lake City, Utah, 84108	(801) 588-6200

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Watson Laboratories, Inc.
417 Wakara Way
Salt Lake City, Utah 84108

2. TELEPHONE NUMBER *(Include Area Code)*

(801) 588-6200

3. PRODUCT NAME

Alora

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. Yes

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

—

6. LICENSE NUMBER / NDA NUMBER

N021310

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

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

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

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

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

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

TURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Cheri R. Fetterhoff for Dorothy Frank	Dorothy A. Frank Director, Regulatory Affairs	December 30, 2000

FORM FDA 3397 (5/98)

Patent Information

(21 U.S.C. 355(b) or (c))

ORIGINAL

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

19 October, 2001

Division of Metabolic and Endocrine Drug Products (HFD- 510)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Document Room 14-B-19
5600 Fishers Lane
Rockville, MD 20857

21 000 BC
ORIG AMENDMENT

RE: NDA 21-310, Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day – Response to request for CMC information

In response to a telephone inquiry on October 18 of this year by Dr. Elsbeth Chikale regarding the Chemistry review of NDA 21-310, we are providing the following information.

A. Dr. Chikale requested that Watson provide a calculation for Expected Introduction Concentration (EIC) for the Environmental Assessment.

The estimated annual consumption of estradiol for the entire Alora product line is [redacted] This includes the three approved sizes and the proposed 9 cm^2 size. In accordance with the FDA guidance document *Environmental Assessment of Human Drug and Biologics Applications* (July 1998), the EIC is:

[redacted]

which is well below the guidance document's minimum threshold of 1 ppb.

B. Dr. Chikale requested clarification regarding Watson's intentions for the use [redacted] in the drug product formulation.

Watson does not intend to use [redacted] in the product formulation.

We trust this provides sufficient information to permit continued review of this NDA. If you have any questions or need any additional information, please feel free to contact me by telephone at (801) 588-6200 or by fax at (801) 583-8135.

Best Regards,

Dorothy A. Frank

Dorothy A. Frank, M.S., R.A.C.
Executive Director, Proprietary Regulatory Affairs

Patent Information Certification

In accordance with 21 CFR § 314.53 (d) (2) ii, Watson Laboratories, Inc. is providing the following identification of patents that claim our drug product Alora® Estradiol Transdermal Systems, which are the subject of this application to add a new indication.

Patent Number (Exp. Date)	Title	Patent Owner
5,122,383 (5/17/2011)	Sorbitan Esters as Skin Permeation Enhancers	Watson Pharmaceuticals, Inc.
5,164,190 (12/11/2010)	Subsaturated Transdermal Drug Delivery Device Exhibiting Enhanced Drug Flux	Watson Pharmaceuticals, Inc.
5,212,199 (5/17/2011)	Sorbitan Esters as Skin Permeation Enhancers	Watson Pharmaceuticals, Inc.
5,227,169 (5/17/2011)	Sorbitan Esters as Skin Permeation Enhancers	Watson Pharmaceuticals, Inc.

Dorothy A. Frank Date: 12 January 2001

Dorothy Frank
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 21-310 SUPPL #

Trade Name Alora Generic Name Estradiol Transdermal System

Applicant Name Watson Laboratories, Inc. HFD- 510

Division Division of Metabolic and Endocrine Drug Products

Approval Date April 5, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X_/

      If yes, what type(SE1, SE2, etc.)?

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

      YES /_X_/ NO /___/

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

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

data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

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

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

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES /_X_/ NO /___/

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

NDA # 21-167, 20-323/S-023
Vivelle (estradiol transdermal system)

NDA #

NDA #

2. Combination product.

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

YES /___/ NO /_X_/

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

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /__/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

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

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

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

YES /___/ NO /_X_/

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

YES /___/ NO /_X_/

If yes, explain:

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

YES /___/ NO /_X_/

If yes, explain:

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

Investigation #1, Study # 1996023 "A Randomized, Double-Blind, Placebo-Controlled, 24-Month, Dose-Ranging, Multi-Center Study Comparing EMTDS to Placebo in the Prevention of Bone Loss in Hysterectomized Postmenopausal Women"

Investigation #2, Study #

Investigation #3, Study #

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

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

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more

investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # _1996023 "A Randomized, Double-Blind, Placebo-Controlled, 24-Month, Dose-Ranging, Multi-Center Study Comparing EMTDS to Placebo in the Prevention of Bone Loss in Hysterectomized Postmenopausal Women"_

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the

conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

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

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____

_____	!	_____
_____	!	_____

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

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

cc:
Archival NDA
HFD-510/Division File
HFD-510/RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

David Orloff
4/5/02 01:16:13 PM

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Debarment Certification

(FD&C Act 306(k)(1))

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Debarment Certification

Watson Laboratories, Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Sec. 306(a) or (b) of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Dorothy A. Frank

Date: 12 January 2001

Dorothy A. Frank, M.S., R.A.C.
Director, Regulatory Affairs

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ON ORIGINAL

Financial Information

(21 CFR 314.50 Part 54)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Protocol 1996023

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical investigators	
See Attached List	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Dorothy Frank	Director, Regulatory Affairs
FIRM/ORGANIZATION	
Watson Laboratories, Inc.	
SIGNATURE	DATE
Dorothy A. Frank	04 December 2000

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address in the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14[illegible]
Rockville, MD 20857

FORM FDA 3454 (3/99)

WITHHOLD 4 PAGE (S)

MEMORANDUM

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

DATE: March 11, 2002

TO: File
NDA 21-310, Alora® (estradiol transdermal system)

FROM: Samuel Wu, Regulatory Project Manager

SUBJECT: **Safety Update**

The firm responded to our November 16, 2001, approvable letter on November 19, 2001. However, there was no information on safety update included in the submission, as requested in the approvable letter.

In the November 15, 2001, submission, firm stated that there were no ongoing studies for the osteoporosis indication and thus no further safety data would be available. This submission satisfies the requirement for submitting safety update in response to our November 16, 2001, approvable letter.

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/s/

Samuel Wu
3/28/02 02:53:03 PM
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-310

FEB 19 2002

Watson Laboratories, Inc.
Attention: Dorothy A. Frank, M.S., R.A.C.
Executive Director, Proprietary Regulatory Affairs
417 Wakara Way
Salt Lake City, UT 84108

Dear Ms. Frank:

We acknowledge receipt on February 6, 2002, of your February 5, 2002, resubmission to your new drug application (NDA) for Alora (Estradiol Transdermal System), 0.025 mg/day, 0.05 mg/day, and 0.075 mg/day.

This resubmission contains additional labeling information submitted in response to our January 18,2002, approvable letter.

We consider this a complete class 1 response to our action letter. Therefore, the user fee goal date is April 6, 2002.

If you have any questions, call me at 301-827-6416.

Sincerely,

{See appended electronic signature page}

Samuel Y. Wu, Pharm.D.
Regulatory Project Management
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Samuel Wu
2/19/02 04:42:13 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-310

Watson Laboratories, Inc.
Attention: Dorothy A. Frank, M.S., R.A.C.
Executive Director, Proprietary Regulatory Affairs
Research Park
417 Wakara Way
Salt Lake City, UT 84108

Dear Ms. Frank:

We acknowledge receipt on November 20, 2001, of your November 19, 2001, resubmission to your new drug application (NDA) for Alora (Estradiol Transdermal System), 0.025 mg/day, 0.05 mg/day, and 0.075 mg/day.

This resubmission contains additional labeling information submitted in response to our November 16, 2001, approvable letter.

We consider this a complete class 1 response to our action letter. Therefore, the user fee goal date is January 20, 2002.

If you have any questions, call me at 301-827-6416.

Sincerely,

{See appended electronic signature page}

Samuel Y. Wu, Pharm.D.
Regulatory Project Management
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Samuel Wu
11/30/01 11:43:59 AM

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MEMORANDUM

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

DATE: February 20, 2001

TO: NDA 21-310

FROM: Randy Hedin

SUBJECT: User Fee for NDA 21-310, Alora (estradiol transdermal system)

I spoke with Cherri Petrie, Manager, Regulatory Affairs, of Watson Laboratories, a variety of times during the past two weeks concerning the user fee submitted for NDA 21-310. I also referred to conversations between her and Mike Jones of the FDA in September of 2000, in which it was discussed if the application should be a supplement, a type 6 NDA, or a type 3 NDA, and the user fee ramifications for each. It was stated at that time, because Watson Laboratories has an approved application for Alora and per our bundling policy, they could submit the application as a supplement and pay the supplement fee (both the strength and indication would be bundled). However, for our own administrative convenience, we would like a new NDA submitted to the Division of Metabolic and Endocrine Drug Products, and we would assess a supplement fee for the new NDA.

I explained to Ms. Petrie that what was not brought up in the September 2000, conversation is that the firm is seeking [redacted] A treatment study is the only study submitted in the NDA. [redacted] The firm submitted an amendment to the NDA on February 14, 2001, withdrawing the [redacted] (see attached letter).

APPEARS THIS WAY
ON ORIGINAL

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

February 14, 2000

John K. Jenkins, M.D., Director
Division of Metabolic and Endocrine
Drug Products (HFD- 510)
CDER, Document Room 14-B-19
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-310 Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day

Dear Dr. Jenkins:

In accordance with the Federal Food, Drug, and Cosmetic Act, Watson Laboratories, Inc. is submitting an amendment to our New Drug Application for a new system size and indication for Alora Estradiol Transdermal Systems. Alora is also subject of our NDA — that was reviewed and approved by the Division of Reproductive and Urologic Drug Products. Three dosage strengths, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day are approved in NDA — for the treatment of moderate to severe vasomotor symptoms associated with menopause.

This amendment is submitted to withdraw the words " —— ;" from the indication proposed in our original submission for 0.025 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day Alora Estradiol Tranedermal Systems. The new proposed indication is "prevention of postmenopausal osteoporosis".

If you have any questions or need any additional information, please feel free to contact me by telephone at (801) 588-6200 or by fax at (801) 583-8135.

Sincerely,

Dorothy A. Frank, M.S., R.A.C.
Director, Regulatory Affairs

Desk copy: Randy Hedin

Research Park, 417 Wakara Way, Salt Lake City, UT 84108 • Tel: 801/588-6200 • Fax: 801/583-6042

/s/

Randy Hedin
2/20/01 04:01:52 PM
CSO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-310

Watson Laboratories, Inc.
Attention: Dorothy A. Frank, M.S., R.A.C.
Director, Regulatory Affairs
417 Wakara Way
Salt Lake City, Utah 84106

Dear Ms. Frank:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Alora® (estradiol transdermal system) 0.025 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day
Review Priority Classification:	Standard (S)
Date of Application:	January 12, 2001
Date of Receipt:	January 16, 2001
Our Reference Number:	NDA 21-310

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 17, 2001, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be November 16, 2001, and the secondary user fee goal date will be January 16, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632).

We note that you have requested a waiver of the pediatric study requirement. We will make a determination whether to grant or deny the request during the review of the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Randy Hedin, R.Ph.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Randy Hedin
1/23/01 12:33:19 PM

APPEARS THIS WAY
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Meeting Date: February 28, 2001 Time: 11:00 - 11:30 PM Location: 17B-43

NDA 21-310 Alora (estradiol transdermal system)

Type of Meeting: Filing Meeting

External participant: None

Meeting Chair: Dr. Colman

External participant lead: None

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Eric Colman, M.D., Clinical Team Leader, DMEDP
Patricia Beaston-Wimmer, M.D., Ph.D., Clinical Reviewer, DMEDP
Karen Davis-Bruno, Ph.D., Pharmacology Team Leader, DMEDP
Hae-Young Ahn, Ph.D., Team Leader, OCPB
Robert Shore, Ph.D., Reviewer, OCPB
Elsbeth Chikhale, Ph.D., Reviewer, DNDCII
Todd Sahlroot, Ph.D., Team Leader, DOBII
Dornette Spell-Lesane, Regulatory Project Manager, DRUDP
Randy Hedin, R.Ph. Senior Regulatory Management Officer, DMEDP

External participant Attendees and titles:

None

Meeting Objectives:

To determine if NDA 21-310 will be filed, and discuss plans for the review of the NDA.

Discussion Points:

- Chemistry: The application is fileable.
- Pharmacology not The application is fileable. However, preclinical data has been submitted for review.
- Biopharm: The application is fileable.

- Statistics: The application is fileable.
- Clinical: The application is fileable.

Decisions (agreements) reached:

- The application will be filed.
- The application does contain financial disclosure information.
- The review will be done as a standard review. The goal to finish the reviews with team leader sign-off is October 9, 2001.
- The application will not be discussed at an Advisory Committee meeting.
- A DSI audit will not be requested.
- The user fee goal dates are:
  - 10 Month: November 16, 2001
  - 12 Month: January 16, 2002

Unresolved or issues requiring further discussion:

- None

Action Items:

- Schedule status meetings as appropriate.

Signature, minutes preparer:_____

Concurrence Chair:_____

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/s/

Randy Hedin
4/9/01 10:29:04 AM

Eric Colman
4/18/01 08:13:18 AM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA #: 21-310 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: January 16, 2001 Action Date: AP: April 5, 2002

HFD 510 Trade and generic names/dosage form: Alora (estradiol transdermal system)

Applicant: Watson Laboratories, Inc. Therapeutic Class: Estrogens

Indication(s) previously approved:
1. Treatment of moderate-to-severe vasomotor symptoms associated with the menopause.
2. Treatment of vulvar and vaginal atrophy.
3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.

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

Number of indications for this application(s): 1

Indication #1: Prevention of postmenopausal osteoporosis

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

✓ Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
✓ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other:_____

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

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

☐ **Other:**_____

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

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Reason(s) for deferral:

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

Other:_____

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

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

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Comments:

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

This page was completed by:

{See appended electronic signature page}

Samuel Y. Wu, Pharm.D.
Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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/s/

Samuel Wu
4/8/02 02:02:18 PM
CSO

Samuel Wu
4/8/02 02:05:50 PM
CSO

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MEDICAL TEAM LEADER MEMORANDUM

DATE: October 12, 2001

NDA: 21-310

DRUG: Alora (transdermal 17β-estradiol)

INDICATION: Prevention of postmenopausal osteoporosis

COMPANY: Watson

PRIMARY REVIEWER: Patricia Beaston-Wimmer, MD, PhD

Background

Transdermal Alora, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day, is currently approved for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause, the treatment of vulval and vaginal atrophy, and the treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. In this supplemental NDA, Watson is seeking approval of 0.025 mg/day, 0.05 mg/day, and 0.075 mg/day of Alora for the prevention of postmenopausal osteoporosis (PMO). In support of approval, the company conducted a 2-year, randomized, double-blind, placebo-controlled trial of postmenopausal women with lumbar spine (LS) bone mineral density (BMD) as the primary endpoint.

Overview of Clinical Trial

Three hundred fifty-five postmenopausal (natural or surgical), hysterectomized women, aged 26 to 69 years, with a mean LS T-score of –0.64 (range –2.7 to 3.8) were randomized in equal fashion to one of four treatment groups: placebo or Alora 0.025 mg/day, 0.05 mg/day, or 0.075 mg/day. All subjects received 1000 mg/day of oral calcium supplementation. The primary endpoint was the change from baseline to Year 2 in LS BMD, the standard endpoint for estrogens seeking a prevention of PMO indication.

There were no statistically significant differences between the Alora and placebo groups for baseline demographic characteristics. Eighty-seven percent of the women were Caucasian, the mean age was about 53 years, the average BMI was 28.5 kg/m^2, the average number of years since hysterectomy was 16, and the mean baseline LS T-score was –0.6. Approximately 67% of placebo-treated subjects and 50% of Alora-treated subjects completed the 2-year study. Over 80% of placebo subjects had at least one post-baseline BMD measurement, while about 70% of the Alora-treated women had at least one on-study BMD assessment. Protocol violations were evenly distributed among the treatment groups and were unlikely to have affected the primary outcome of the study.

In the assessment of the change in LS BMD from baseline to Endpoint, the placebo group had a mean percent decrease in BMD of 0.8%, whereas the Alora 0.025 mg/day, 0.05 mg/day, and 0.075 mg/day groups had mean percent increases of 1.4%, 3.4%, and 4.2%, respectively ($p<0.01$ for all comparisons of Alora vs. placebo). The placebo-subtracted changes in LS BMD for the Alora groups are similar to equivalent doses of other approved transdermal estrogens.

Aside from a higher incidence of moderately severe application site skin reactions in the Alora vs. placebo groups, the reporting of clinical adverse events was what one would expect for a transdermal estrogen product (i.e., breast pain). There were no significant differences between active- and placebo-treated groups in the reporting of laboratory abnormalities or vital signs.

Comment

Watson has provided adequate data to support approval of 0.025 mg, 0.050 mg, and 0.075 mg/day of their transdermal 17β-estradiol, Alora, for the prevention of PMO. Compared with placebo, there was a more-or-less dose-related increase in LS BMD in the active-treatment groups, with the lowest dose (0.025 mg) increasing mean LS BMD by approximately 2.0%.

In hindsight, there were three features of the Alora clinical trial that were less than ideal. First, some of the women had non-osteopenic LS BMD values (i.e., greater than –1.0). It would have been more appropriate to limit the inclusion of women with T-scores in the osteopenic range (-1.0 to –2.5). Second, all of the study participants had undergone an hysterectomy; therefore, there was no need to study the effect of Alora plus a progestin on BMD. Progestins may attenuate the affect of estrogens on BMD – this will be pointed out in the labeling. And third, the 1000 mg per day supplementation of calcium was probably sub-optimal for most study subjects. None of these facts preclude approval of Alora, however.

In anticipation of reaching agreement with Watson on final labeling, I, like Dr. Beaston-Wimmer, recommend that the 0.025 mg, 0.05 mg, and 0.075 mg/day doses of Alora be approved for the prevention of PMO.

Eric Colman, MD

I concur Dr. Colman's recommendation

2/3/

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Eric Colman
10/17/01 02:20:49 PM
MEDICAL OFFICER

David Orloff
10/22/01 04:28:25 PM
MEDICAL OFFICER
Concur with Drs. Colman and Beaston-Wimmer. There will be no separate Division Director memo. DGO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-310

CORRESPONDENCE

MESSAGE CONFIRMATION

01/18/02 18:57

DATE	TIME	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
01/18	18:40	09'54"	8015838135	•CALLING	30	OK	0000

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APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Division of Metabolic and Endocrine
Drug Products, HFD-510
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 18, 2002

To: John Smith	From: Samuel Wu
Company: Watson Labs.-Utah	Division of Metabolic and Endocrine Drug Products
Fax number: 801-583-8135	Fax number: (301) 443-9282
Phone number: 801-588-6377	Phone number: 301-827-6416
Subject: Approvable Letters for Alora	
Total no. of pages including cover: 29	

Comments: DMEDP cover letter
ORUDP cover letter
PI/PPI

Document to be mailed: ☒ YES ☑ NO

APPEARS THIS WAY
ON ORIGINAL

MESSAGE CONFIRMATION

04/05/02 16:34
ID=DMEDP-CDER-FDA

NO.	MODE	BOX	GROUP
319	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
04/05 5:33	01'20"	8015838135	004/004	OK		0000

Called Sherry Petrie
@ 2:45 pm
801-588-6633

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: April 5, 2002

To: Dorothy A. Frank	**From:** Samuel Y. Wu
Company: Watson Laboratories	Division of Metabolic and Endocrine Drug Products
Fax number: 801-583-8135	**Fax number:** 301-443-9282
Phone number: 801-588-6200	**Phone number:** 301-827-6416

Subject: NDA 21-310; Alora (estradiol transdermal system) Approval

Total no. of pages including cover: 4

Comments:

The labeling (package insert and patient package insert) will be included in the fax from DRUDP.

Document to be mailed: ✔ YES ☐ NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: April 5, 2002

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Subject: NDA 21-310; Alora (estradiol transdermal system) Approval

Total no. of pages including cover: 4

Comments:

The labeling (package insert and patient package insert) will be included in the fax from DRUDP.

Document to be mailed: ✔YES ☐NO

DUPLICATE

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

February 5, 2002

Division of Metabolic and
Endocrine Drug Products (HFD- 510)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Document Room 14-B-19
5600 Fishers Lane
Rockville, MD 20857

Response to Approvable Letter

AL
N 000
ORIG AMENDMENT

RE: **NDA 21-310,** Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day
Response to Approvable Letter

Watson submits the enclosed information in response to FDA's approvable letter dated January 18, 2002, requesting revisions to the labeling for Alora. For both the package insert and the patient insert, we have included a copy of our proposed version, with the changes indicated.

The enclosed version, with the exception of minor typographical corrections, includes all of FDA's requested revisions, as well as all of the requested additional information.

We have modified Table 3 (vasomotor symptom reduction), in accordance with your request. The supporting efficacy data are enclosed, on a CD. Further explanatory text for these changes follows:

> As per the Statistical Analysis Plan for this study, efficacy was assessed in terms of the mean % reduction in frequency of moderate/severe hot flushes from baseline. The values reported in the previously proposed labeling were calculated from the mean data for the non-LOCF data presented in Table 21of the Clinical Trial Report (NDA #20-655, Section 8, Volume VI, page 0085). However, the LOCF data should have been reported to correspond with the existing approved labeling for Alora.
>
> The mean changes in frequency of moderate/severe hot flushes (LOCF data) are reported in Appendix C.4.12 of the Clinical Trial Report (NDA #20-655, Section 8, Volume XII, pages 0046-0051) and the amended table is shown in the enclosed package insert.

We believe this submission meets the labeling recommendations of the Agency for this product.

Research Park, 417 Wakara Way, Salt Lake City, UT 84108 • Tel: 801/588-6200 • Fax: 801/583-6042

Regarding your request for additional safety and effectiveness information, there is no additional information pertaining to safety or effectiveness. Other than the study that was the subject of this NDA, there are no additional studies.

Please note that your approvable letter omitted the 0.1 mg/day strength; please include this strength in the prevention of osteoporosis indication when approval is issued.

We look forward to your prompt response. If you have any questions, please call John Smith, Regulatory Manager, at (801) 588-6377.

Best Regards,

Dorothy A. Frank

Dorothy A. Frank, M.S., R.A.C.
Executive Director,
Proprietary Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Watson Laboratories, Inc.	February 5, 2002
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
(801) 588-6200	(801) 583-8135
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
417 Wakara Way Salt Lake City, Utah 84108	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-310

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Estradiol Transdermal System (EMTDS)	Alora® Estradiol Transdermal System

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Estra-1,3,5 (10)-triene-3, 17-diol	None

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Transdermal System	0.025, 0.05, 0.075 and 0.1 mg/day	Transdermal

(PROPOSED) INDICATION(S) FOR USE: Treatment of moderate-to-severe vasomotor symptoms associated with menopause. Treatment of vulval and vaginal atrophy. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. Prevention of postmenopausal osteoporosis.

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Response to Approvable Letter

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*

☐	1. Index	
☒	2. Labeling *(check one)*	☒ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50(c))	
☐	4. Chemistry section	
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)	
☐	B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)	
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☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)	
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))	
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)	
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)	
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)	
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)	
☐	12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)	
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))	
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A)	
☐	15. Establishment description (21 CFR Part 600, if applicable)	
☐	16. Debarment certification (FD&C Act 306(k)(1))	
☐	17. Field copy certification (21 CFR 314.50(k)(3))	
☐	18. User Fee Cover Sheet (Form FDA 3397)	
☐	19. Financial Information (21 CFR Part 54)	
☐	20. OTHER *(Specify)*	

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Dorothy A. Frank	Dorothy A. Frank, M.S., R.A.C. Executive Director, Proprietary Regulatory Affairs	February 5, 2002

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
417 Wakara Way Salt Lake City, Utah, 84108	(801) 588-6200

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

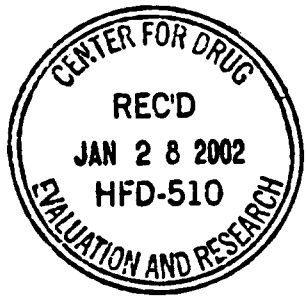
ORIGINAL

WATSON Laboratories, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

N 0000
NEW CORRESP

January 25, 2002



Division of Metabolic and Endocrine Drug Products (HFD- 510)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Document Room 14-B-19
5600 Fishers Lane
Rockville, MD 20857

RE: **NDA 21-310,** Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day
Response to Approvable Letter

In response to FDA's approvable letter dated January 18, 2002, Watson is notifying the Division that we intend to file an amendment to the NDA.

If you have any questions, please call John Smith, Regulatory Manager, at (801) 588-6377.

Best Regards,

Dorothy A. Frank

Dorothy A. Frank, M.S., R.A.C.
Executive Director,
Proprietary Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Research Park, 417 Wakara Way, Salt Lake City, UT 84108 • Tel: 801/588-6200 • Fax: 801/583-6042

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Watson Laboratories, Inc.	January 25, 2002
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
(801) 588-6200	(801) 583-8135
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
417 Wakara Way Salt Lake City, Utah 84108	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-310

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* Estradiol Transdermal System (EMTDS)

PROPRIETARY NAME *(trade name)* IF ANY Alora® Estradiol Transdermal System

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* Estra-1,3,5 (10)-triene-3, 17-diol

CODE NAME *(If any)* None

DOSAGE FORM: Transdermal System

STRENGTHS: 0.025, 0.05, 0.075 and 0.1 mg/day

ROUTE OF ADMINISTRATION: Transdermal

(PROPOSED) INDICATION(S) FOR USE: Treatment of moderate-to-severe vasomotor symptoms associated with menopause. Treatment of vulval and vaginal atrophy. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. Prevention of postmenopausal osteoporosis.

APPLICATION INFORMATION

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IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Intent to Amend NDA

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

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☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Intnet to Amend NDA

CERTIFICATION

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5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Dorothy A. Frank	Dorothy A. Frank, M.S., R.A.C. Executive Director, Proprietary Regulatory Affairs	January 25, 2002

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
417 Wakara Way Salt Lake City, Utah, 84108	(801) 588-6200

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Department of Health and Human Services
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CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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ORIGINAL

WATSON Laboratories, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

16 January, 2002

Dr. Solomon Sobel, Director
Division of Metabolic and Endocrine Drug Products (HFD- 510)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Document Room 14-B-45
5600 Fishers Lane
Rockville, MD 20857

N 000 C
NEW CORRESP

RE: **NDA 21-310:** Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day

Dr. Sobel:

Based upon our telephone conversations of January 11, 14, 15 and 16 with the Regulatory Project Managers at DMEDP and DRUDP, Watson understands that the package insert for Alora will have further changes requested by FDA, in addition to those requested in the approvable letter of November 16, 2001. It is also our understanding that the statement to be added to the new insert regarding Adhesion, which Watson provided at FDA's request, has proved to be difficult to review within the user fee goal date. To facilitate FDA's approval of the new indication and size within the goal date, Watson makes the following proposal regarding these issues:

1. Watson will accept all of FDA's requested changes to the insert for the Alora product.
2. The statement regarding Adhesion is not particular to the new indication, and is being added at DRUDP's request, to make the labeling conform to the Division's current information requirements. Since the review of this statement appears to be the single issue delaying approval, Watson will withdraw the proposed Adhesion statement from the insert. Watson will also commit to submitting a proposed Adhesion statement, with a detailed supporting rationale, based on the clinical data previously submitted in supplement S003 to NDA 20-655. Watson will submit this in a supplemental NDA within 30 calendar days of receiving an approval letter for the new indication.

There is no reason to delay the approval of the new indication for this product because of questions over adhesion data. The product has been used safely so far without any statements in the insert regarding adhesion. We realize that the Division wants the insert to contain a statement regarding adhesion, and will commit to providing one quickly.

Sincerely,

Dorothy A. Frank, M.S., R.A.C.
Executive Director, Regulatory Affairs

Research Park, 417 Wakara Way, Salt Lake City, UT 84108 • Tel: 801/588-6200 • Fax: 801/583-6042

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Watson Laboratories, Inc.	January 16, 2002
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
(801) 588-6200	(801) 583-8135
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
417 Wakara Way Salt Lake City, Utah 84108	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-310

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* Estradiol Transdermal System (EMTDS)

PROPRIETARY NAME *(trade name)* IF ANY Alora® Estradiol Transdermal System

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* Estra-1,3,5 (10)-triene-3, 17-diol

CODE NAME *(If any)* None

DOSAGE FORM: Transdermal System

STRENGTHS: 0.025, 0.05, 0.075 and 0.1 mg/day

ROUTE OF ADMINISTRATION: Transdermal

(PROPOSED) INDICATION(S) FOR USE: Treatment of moderate-to-severe vasomotor symptoms associated with menopause. Treatment of vulval and vaginal atrophy. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. Prevention of postmenopausal osteoporosis.

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Proposal for Labeling

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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CERTIFICATION

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4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

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The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
for DRF	Dorothy A. Frank, M.S., R.A.C. Executive Director, Proprietary Regulatory Affairs	January 16, 2002

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
417 Wakara Way Salt Lake City, Utah, 84108	(801) 588-6200

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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ORIGINAL

WATSON Laboratories, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

January 14, 2002

NEW CORRESP

Division of Metabolic and Endocrine Drug Products (HFD- 510)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Document Room 14-B-19
5600 Fishers Lane
Rockville, MD 20857

RE: **NDA 21-310,** Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day
Response to request for information

In response to a request for clarifying information, made by Ms. Dornette Spell-LeSane on January 10 of this year, Watson is providing the following information:

The adhesion data for Alora was contained in supplement S003 to NDA 20-655, submitted September 3, 1998 and approved November 24, 1998. The Clinical Report number in that supplement is E97005. This information is the basis of the Adhesion section of the package insert.

If you have any questions, please call John Smith, Regulatory Manager, at (801) 588-6377

Best Regards,

Dorothy A. Frank

Dorothy A. Frank, M.S., R.A.C.
Executive Director,
Proprietary Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Research Park, 417 Wakara Way, Salt Lake City, UT 84108 • Tel: 801/588-6200 • Fax: 801/583-6042

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
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417 Wakara Way Salt Lake City, Utah 84108	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-310

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* Estradiol Transdermal System (EMTDS)

PROPRIETARY NAME *(trade name)* IF ANY Alora® Estradiol Transdermal System

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* Estra-1,3,5 (10)-triene-3, 17-diol

CODE NAME *(If any)* None

DOSAGE FORM: Transdermal System

STRENGTHS: 0.025, 0.05, 0.075 and 0.1 mg/day

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- ☐ 19. Financial Information (21 CFR Part 54)
- ☒ 20. OTHER *(Specify)* Response to Request for Information

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Dorothy A. Frank	Dorothy A. Frank, M.S., R.A.C. Executive Director, Proprietary Regulatory Affairs	January 14, 2002

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
417 Wakara Way Salt Lake City, Utah, 84108	(801) 588-6200

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CBER, HFM-99
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Rockville, MD 20852-1448

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WATSON Laboratories, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

ORIGINAL

N 000 AL
ORIG AMENDMENT

November 19, 2001

Division of Metabolic and Endocrine Drug Products (HFD- 510)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Document Room 14-B-19
5600 Fishers Lane
Rockville, MD 20857

RE: **NDA 21-310,** Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day
Response to Approvable Letter

In response to FDA's approvable letter dated November 16, 2001, in which revisions to the labeling for Alora were requested, Watson hereby submits the enclosed information. For both the package insert and the patient insert, we have included a copy of Watson's proposed version, with notes regarding any changes.

The enclosed version, with the exception of minor typographical errors, includes all of FDA's requested language, as well as all of the additional information requested by FDA. We believe this submission meets the labeling recommendations of the Agency for this product.

Regarding your request for additional safety and effectiveness information, there is no additional information pertaining to safety or effectiveness. Other than the study that was the subject of this NDA, there are no additional studies.

Please note that your approvable letter omitted the 0.1 mg/day strength; please include this strength in the prevention of osteoporosis indication when approval is issued.

We look forward to your prompt response. If you have any questions, please call John Smith, Regulatory Manager, at (801) 588-6377

Best Regards,

Dorothy A. Frank

Dorothy A. Frank, M.S., R.A.C.
Executive Director,
Proprietary Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
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APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Watson Laboratories, Inc.	November 19, 2001
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
(801) 588-6200	(801) 583-8135
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
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PRODUCT DESCRIPTION

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CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* Estra-1,3,5 (10)-triene-3, 17-diol

CODE NAME *(If any)* None

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Transdermal System	0.025, 0.05, 0.075 and 0.1 mg/day	Transdermal

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APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
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REASON FOR SUBMISSION Response to Approvable Letter

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3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Dorothy A. Frank	Dorothy A. Frank, M.S., R.A.C. Executive Director, Regulatory Affairs	November 19, 2001

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
417 Wakara Way Salt Lake City, Utah, 84108	(801) 588-6200

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

November 15, 2001

Division of Metabolic and Endocrine
Drug Products (HFD- 510)
CDER, Document Room 14-B-45
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Response to Request for Information

Re: **NDA 21-310** Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day
Response to Request for Information

Dear Mr. Wu:

Per your telephone conversation with John Smith on November 7, 2001, enclosed please find the requested administrative pieces for FDAs internal files to complete the "action package" for Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day. Your requests are listed below with our response, and this communication is provided by fax to your attention and will be followed by hard copy submission.

- *Please provide copies of the artwork (black and white are fine, or computer printouts) for the pouch label and carton label for the 0.025 mg size.* Copies of the artwork for the .025 mg size pouch label and carton label are provided.

- *Please confirm whether the osteoporosis clinical study was performed under the Alora IND* [redacted] The osteoporosis clinical study was performed under the Alora IND [redacted]

- *Please provide the dates of any end-of-phase 2 or pre-NDA meetings between FDA and Watson regarding the osteoporosis indication.*
  - ➢ End-of-phase 2 meeting on July 31, 1996 included discussion pertaining to the osteoporosis indication.
  - ➢ Teleconference on May 20, 1997 - discussion of the washout period.
  - ➢ Watson requested a pre-NDA meeting with DRUDP & also with DMEDP in April, 2000. FDA held an internal pre-meeting June 15, 2000 and determined that

a face-to-face meeting was not necessary. FDA provided comments in response to our briefing package and questions by fax on June 29, 2001.

- *Please provide a copy of Watson's request for pediatric waiver.* A copy of the pediatric waiver that was submitted in the original application is provided.
- *Are there any ongoing studies for Alora relevant to the osteoporosis indication?* There are no ongoing studies for Alora relevant to osteoporosis indication.

If you have any questions or need any additional information, please contact me by telephone at (801) 588-6200 or by fax at (801) 583-8135.

Sincerely,

Dorothy A. Frank, M.S., R.A.C.
Executive Director,
Proprietary Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL