

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-655/S-008

CORRESPONDENCE


Watson Laboratories-Utah

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FAX

PAGE 1 OF 3

TO:	Dornette Spell-LeSane	
	FDA / CDER / DRUDP	
FAX:	(301) 594-0747	
FROM:	John W. Smith	Direct phone: (801) 588-6377
		e-mail: John.Smith@watsonpharm.com
DATE:	January 16, 2002	

Dornette:

I'm sending you these two pages from the Statistical Analysis Report contained in Protocol E97005, from supplement S003. The first is the summary table of "Percentage of Systems Adhered", which shows the following:

System	Nominal cross-linker content (%)	Overall adherence (%)
<i>Control</i> (the formulation being marketed at the time of the supplement)		
<i>B</i> (the formulation marketed now)		
<i>C</i>		
<i>D</i>		

The second is the table of frequency distributions of adhesion evaluations by system type / application number.

As you know, this was a crossover design, so it is not realistic to say that only a certain number of patients wore the current formulation; all patients wore it at some point in the study.

Best Regards,

 John W. Smith
 Manager, Regulatory Affairs

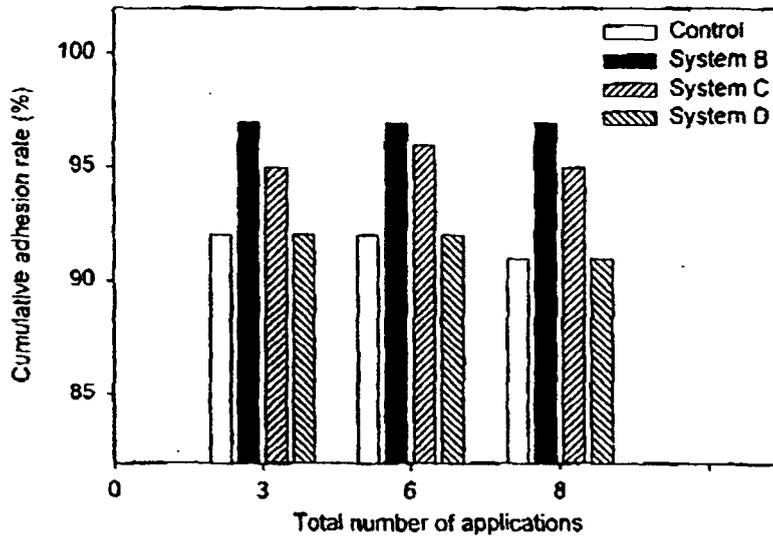
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Table 4: Percentage of Systems Adhered

Application	Control	System B	System C	System D
1	90	96	93	89
2	90	98	97	88
3	92	97	94	95
4	93	97	98	95
5	93	97	95	97
6	94	97	96	91
7	91	99	96	92
8	92	100	98	93
Overall	92	97	96	92

Figure 1: Cumulative adhesion rate after three, six and eight applications



TheraDerm EPMTDS
Protocol E97005Reduced Cross-linker Study
Statistical Analysis ReportTHERATECH
Page 13**Table 6: Frequency Distributions of Adhesion Evaluations by System and Application Number**

Application Number	Adhesion Evaluations	Control		System B		System C		System D	
		N	%	N	%	N	%	N	%
1	On	334	90	117	96	111	93	116	89
	Off	37	10	5	4	8	7	14	11
2	On	334	90	122	98	122	97	107	88
	Off	37	10	3	2	4	3	14	12
3	On	341	92	120	97	118	94	116	95
	Off	31	8	4	3	8	6	6	5
4	On	343	93	120	97	119	98	117	95
	Off	26	7	4	3	3	2	6	5
5	On	341	93	118	97	119	95	112	97
	Off	24	7	4	3	6	5	4	3
6	On	338	94	114	97	115	96	112	91
	Off	22	6	3	3	5	4	11	9
7	On	328	91	115	99	114	96	115	92
	Off	32	9	1	1	6	4	10	8
8	On	331	92	118	100	114	98	116	93
	Off	28	8	0	0	2	2	9	7
Chi-Square	Statistic	0.780		0.569		1.854		3.904	
	P-value	0.677		0.752		0.396		0.142	

* Test of Period effect, for Applications 1, 2 and 3

No period effect was detected for applications 1 through 3 of the test and control systems (Chi-Square test; $p > 0.05$).

Since no period effect was observed, adhesion results from applications 1 through 3 were combined for the following primary analysis.

Frequency distributions for adhesion ("off" or "on") are reported by system and sequence in Table 7 and by system and study center in Table 8. Chi-square tests of the data showed that there were no significant sequence or study center effects on adhesion for the first three applications of any of the systems (all $p > 0.05$).

Division of Reproductive and Urologic Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: 20-655/S-008

Name of Drug: Alora

Sponsor: Watson Laboratories

Material Reviewed:

- Physician Package Insert
- Patient Package Insert

Submission Date(s): February 5, 2002

Receipt Date(s): February 5, 2002

Background and Summary:

The sponsor submitted a supplemental drug application to the Division of Reproductive and Urologic Drug Products on June 12, 2001, in conjunction with their new drug application NDA 21-310 submitted to the division of Metabolic and Endocrine Drug Products on January 12, 2001, for a lower dose strength, for the indication of osteoporosis. The sponsor received an approvable letter on November 16, 2001, and January 18, 2002, with recommended labeling changes. This submission dated February 5, 2002 is in response to the January 18, 2002, approvable letter.

Review

FDA requested labeling changes	Sponsor submission February 5, 2002	Comments
Alora® (estradiol transdermal system) Continuous Delivery for Twice Weekly Dosing	Alora® (estradiol transdermal system) Continuous Delivery for Twice Weekly Dosing	Acceptable
PRESCRIBING INFORMATION	PRESCRIBING INFORMATION	
ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER. Close clinical surveillance of all women taking estrogens is important.	ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER. Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic	Acceptable

**APPEARS THIS WAY
ON ORIGINAL**

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<p>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.</p>	<p>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.</p>	
<p>DESCRIPTION</p> <p>████████████████████ ████████████████████ 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 <i>in vivo</i> 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 cm² and contains 0.75, 1.5, 2.3, and 3.0 mg of estradiol, USP, respectively. The composition of the <u>estradiol transdermal systems per unit</u> ██████████ area is identical. Estradiol, USP is a white, crystalline powder that is chemically described as estra-1,3,5(10)-triene-3, 17β-diol, has an empirical formula of C₁₈H₂₄O₂ and has molecular weight of 272.39. The structural formula is:</p>	<p>DESCRIPTION</p> <p>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 <i>in vivo</i> 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 cm² 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, 17β-diol, has an empirical formula of C₁₈H₂₄O₂ and has molecular weight of 272.39. The structural formula is:</p>	<p>Acceptable</p>
<p>████████████████████ Alora ██████████ consists of three layers. Proceeding from the polyethylene backing film as shown</p>	<p>Alora consists of three layers. Proceeding from the polyethylene backing film as shown in the cross-sectional view below, the adhesive matrix</p>	<p>Acceptable</p>

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<p>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.</p>	<p>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.</p>	
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<p>CLINICAL PHARMACOLOGY</p> <p>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 and estrogen replacement therapy acts to reduce the elevated levels of these hormones seen in postmenopausal women.</p>	<p>CLINICAL PHARMACOLOGY</p> <p>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 and estrogen replacement therapy acts to reduce the elevated levels of these hormones seen in postmenopausal women.</p>	<p>The final sentence of this section should be changed as follows: <u>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.</u></p>
<p>Pharmacokinetics</p>	<p>Pharmacokinetics</p>	

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<p>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.</p>	<p>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.</p>	<p>The extra space between the words "orally" and "administered" should be removed</p>
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ON ORIGINAL**

<p>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.</p> <p>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 <i>in vivo</i> 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.</p> <p>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.</p>	<p>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.</p> <p>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 <i>in vivo</i> 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.</p>	<p>Acceptable</p>
<p>Figure 1 Mean steady state estradiol serum</p>	<p>Figure 1 Mean steady state estradiol serum concentration</p>	

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<p>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.</p> <p>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.</p> <p>Table 1 provides a summary of the estradiol pharmacokinetic parameters studied during biopharmaceutic evaluation of Alora.</p>	<p>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.</p> <p>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.</p> <p>Table 1 provides a summary of the estradiol pharmacokinetic parameters studied during biopharmaceutic evaluation of Alora.</p>	
<p>Table 1</p> <p>Mean (SD) Pharmacokinetic Profile of Alora Over an 84-Hour Dosing Interval</p> <p>Steady state estradiol serum concentrations were measured in the 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.</p>	<p>Table 1</p> <p>Mean (SD) Pharmacokinetic Profile of Alora Over an 84-Hour Dosing Interval</p> <p>Steady state estradiol serum concentrations were measured in the 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.</p>	
<p>Table 2</p> <p>Mean (SD) steady-state estradiol serum concentrations (pg/ml) in</p>	<p>Table 2</p> <p>Mean (SD) steady-state estradiol serum concentrations (pg/ml) in clinical trials of 3</p>	<p>Acceptable</p>

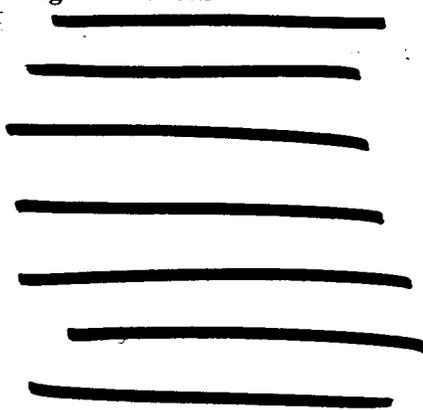
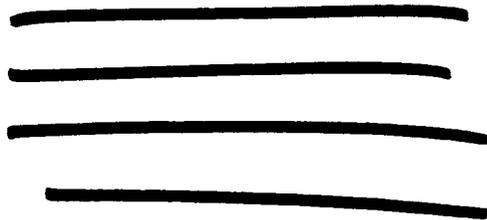
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<p>clinical trials of 3 month (Studies 1 and 2) and 2 year (Study 3) duration In a 2-year, randomized, double-blind, placebo-controlled, prevention of postmenopausal osteoporosis study in 355 hysterectomized women, the average baseline-adjusted steady-state 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.</p>	<p>month (Studies 1 and 2) and 2 year (Study 3) duration</p>	<p style="text-align: center;"> </p>
<p>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. [REDACTED]</p>	<p>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. [REDACTED]</p>	<p>[REDACTED]</p> <p><u>Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.</u></p>
<p>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</p>	<p>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</p>	<p>[REDACTED]</p>

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<p>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.</p>	<p>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.</p>	
<p>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.</p>	<p>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.</p>	

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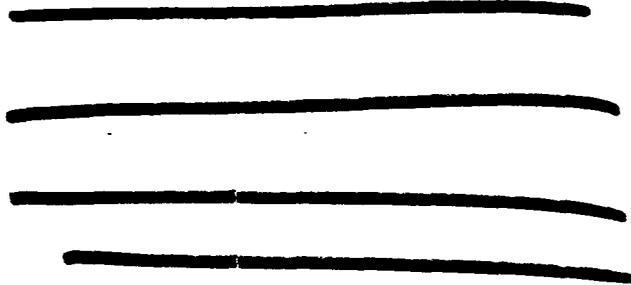
<p>Special Populations Alora has been studied only in healthy postmenopausal women (approximately 90% Caucasian). There are no long term studies in postmenopausal women with an intact uterus. No pharmacokinetic studies were conducted in other special populations, including patients with renal or hepatic impairment.</p>	<p>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.</p>	
<p>Drug Interactions </p>	<p>Drug Interactions </p>	<p>The two sentences in this subsection should be deleted and replaced with the following language: <u><i>In vitro</i> and <i>in vivo</i> 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, carbamazepine, and rifampin 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 erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens</u></p>

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<p>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.</p> <p>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 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 and 12 for relief of both the frequency and severity of vasomotor symptoms .</p>	<p>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.</p> <p>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 and 12 for relief of both the frequency and severity of vasomotor symptoms .</p>	<p>The last sentence should be modified with removal of (see Table 3) from the end of the sentence to follow the word frequency. The sentence should read as follows: <u>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.</u></p>
<p>Table 3</p> <p>Mean Change from Baseline in Frequency of Moderate-to-Severe Vasomotor Symptoms for Alora Compared to Placebo</p>	<p>Table 3</p> <p>Mean Change from Baseline in Frequency of Moderate-to-Severe Vasomotor Symptoms for Alora Compared to Placebo</p>	<p>Add the letters "ITT" after placebo</p>

FDA requested that sponsor provide data to support Table 3

Sponsor revised table and data as follows:



Following Biometrics review of the SAS data sets, a new table was made based on an ANCOVA model with adjustments of the means using the factors of treatment and baseline with the ITT population. FDA is recommending that Table 3 be replaced as follows:

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.

<p>██████████ ██████████ ██████████ ██████████ 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 ██████████.</p>	<p>██████████ ██████████ 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,</p>	<p>Change to "Effects on vulvar <u>and</u> vaginal atrophy"</p>
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<p>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.</p>	<p>respectively. Corresponding reductions in basal/parabasal and intermediate cells were also observed.</p>	
<p>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.</p>	<p>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.</p>	<p>Acceptable</p>
<p>Figure 3</p>	<p>Figure 3</p>	<p>Acceptable by DMEDP</p>

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<p><u>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)</u></p> <p>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.</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>-All</p> <p><u>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.</u></p>	<p><u>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)</u></p> <p>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.</p> <p>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.</p>	
<p>INDICATIONS AND USAGE Alora is indicated in:</p>	<p>INDICATIONS AND USAGE Alora is indicated in:</p>	

Treatment of moderate-to-severe vasomotor symptoms associated with the menopause.
Treatment of vulvar and vaginal atrophy.
3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
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.

[REDACTED]

The mainstays of prevention of postmenopausal osteoporosis are weight-bearing exercise, adequate calcium and vitamin D

Treatment of moderate-to-severe vasomotor symptoms associated with the menopause.
Treatment of vulvar and vaginal atrophy.
3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
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.

Under **INDICATIONS AND USAGE**, 4. Prevention of postmenopausal osteoporosis, the comma following the word intake in the third sentence should be deleted. The sentence should read as follows::
The mainstays of prevention of postmenopausal osteoporosis are weight-bearing exercise, adequate calcium and vitamin D intake

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<p><u>intake, and, when indicated, estrogen.</u> 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 USA 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.</p> <p><u>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).</u></p>	<p>Postmenopausal women absorb dietary calcium less efficiently than premenopausal women and require an average of 1500 mg of elemental calcium to remain in neutral calcium balance. The average calcium intake in the US is 400-600 mg. 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.</p> <p>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).</p>	<p><u>and, when indicated, estrogen.</u></p> <p>In sentence 4 and 5 mg/d should be changed to mg/day and kept consistent with the 6th sentence /</p>
<p>CONTRAINDICATIONS Estrogens should not be used in individuals with any of the following conditions:</p> <ol style="list-style-type: none"> 1. Known or suspected pregnancy 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; 	<p>CONTRAINDICATIONS Estrogens should not be used in individuals with any of the following conditions:</p> <ol style="list-style-type: none"> 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 	<p>CONTRAINDICATIONS</p> <p>Change 1. "Known or suspected pregnancy; see PRECAUTIONS. Estrogens may cause fetal harm when administered to a pregnant woman".as follows:</p> <ol style="list-style-type: none"> 1. Known or suspected pregnancy. See PRECAUTIONS. Estrogens may cause fetal harm when

<p>4. Known or suspected estrogen-dependent neoplasia; Active [redacted] [redacted] deep vein thrombosis/pulmonary embolism or a history of these conditions. Known hypersensitivity to any of the components of Alora.</p>	<p>estrogen-dependent neoplasia; Active deep vein thrombosis/pulmonary embolism or a history of these conditions. Known hypersensitivity to any of the components of Alora.</p>	<p>administered to a pregnant woman.</p>
<p>WARNINGS</p> <p>1. Induction of [redacted] Malignant Neoplasms.</p> <p>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 [redacted] years after estrogen therapy is discontinued..</p> <p>b. Breast cancer. While some epidemiologic studies suggest a very modest increase in breast</p>	<p>WARNINGS</p> <p>1. Induction of Malignant Neoplasms.</p> <p>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 [redacted] years after estrogen therapy is discontinued..</p> <p>b. Breast cancer. While some epidemiologic studies suggest a very modest increase in breast cancer risk for estrogen-alone</p>	<p>WARNINGS</p> <p>1. Induction of Malignant Neoplasms.</p> <p>a. Endometrial cancer In the first sentence [redacted] should be changed to <u>2 to 12-fold</u></p> <p>In the third sentence "15- to 24-fold" should be changed to <u>15 to 24-fold</u>.</p> <p>In the last sentence [redacted] should be changed to <u>8 to 15</u></p> <p>[redacted]</p> <p>In the second sentence change [redacted] to <u>24 to 40%</u></p>

<p>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 1.5-2.0), although this is based solely on epidemiologic studies, and definitive conclusions await prospective, controlled clinical trials.</p>	<p>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 1.5-2.0), although this is based solely on epidemiologic studies, and definitive conclusions await prospective, controlled clinical trials.</p>	
<p>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</p>	<p>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</p>	

<p>perform monthly breast-self examinations. In addition, mammography examinations should be scheduled as suggested by providers based on patient age and risk factors.</p> <p>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.</p> <p><i>Venous thromboembolism.</i> 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</p>	<p>examinations should be scheduled as suggested by providers based on patient age and risk factors.</p> <p>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.</p> <p><i>Venous thromboembolism.</i> 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</p>	<p>Acceptable</p>
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<p>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 <u>2 to 3</u> cases per 10,000 women per year.</p> <p>Cerebrovascular disease. Embolic cerebrovascular events have been reported in <u>postmenopausal</u> women receiving estrogens.</p> <p>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.</p> <p>3. Gallbladder </p>	<p>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.</p> <p>Cerebrovascular disease. Embolic cerebrovascular events have been reported in postmenopausal women receiving estrogens.</p> <p>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.</p> <p>3. Gallbladder Disease. A 2- to 4-fold increase in the risk of gallbladder disease</p>	<p>Acceptable</p> <p>Acceptable</p> <p>3. Gallbladder Disease "2- to 4-fold" should be changed to <u>2 to 4-fold</u></p>
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<p> <u>Disease</u>. A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in <u>postmenopausal</u> women receiving [REDACTED] [REDACTED] [REDACTED] [REDACTED] <u>-estrogens</u> has been reported. </p> <p> 4. Hypercalcemia. [REDACTED] <u>Estrogen</u> 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. </p>	<p> requiring surgery in postmenopausal women receiving estrogens has been reported. </p> <p> 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. </p>	<p>Acceptable</p>
<p>PRECAUTIONS</p> <p>A. General</p> <p>1. <i>Addition of a progestin when a woman has not had a hysterectomy.</i> 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.</p> <p>There are, however, possible risks that may be associated with the use of progestins in estrogen replacement regimens. These include: [REDACTED] adverse effects on lipoprotein</p>	<p>PRECAUTIONS</p> <p>A. General</p> <p>1. <i>Addition of a progestin when a woman has not had a hysterectomy.</i> 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.</p> <p>There are, however, possible risks that may be associated with the use of progestins in estrogen replacement regimens. These include: adverse effects on</p>	<p>PRECAUTIONS</p> <p>A. General</p> <p>1. <i>Addition of a progestin when a woman has not had a hysterectomy.</i> The following sentence should be added to follow the first sentence which begin with Studies and ends with alone. <u>Endometrial hyperplasia may be a precursor to endometrial cancer.</u></p> <p>Remove the colon following the word include in the following sentence "These include: adverse effects on lipoprotein metabolism (e.g.,</p>

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<p>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.</p> <p>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 post-menopausal 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.</p> <p>3. Elevated blood pressure. In a small number of case reports, substantial increases in blood pressure during estrogen replacement therapy have been attributed to</p>	<p>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.</p> <p>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 post-menopausal 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.</p> <p>3. Elevated blood pressure. In a small number of case reports, substantial increases in blood pressure during estrogen replacement therapy have been attributed to</p>	<p>lowering HDL and raising LDL) and impairment of glucose tolerance.”</p> <p>2. Cardiovascular risk</p> <p>In sentence 2 and sentence 3 change “post-menopausal” to <u> </u></p> <p>Acceptable</p>
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<p>idiosyncratic reactions to estrogens. In a large, randomized, placebo controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen.</p>	<p>idiosyncratic reactions to estrogens. In a large, randomized, placebo controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen.</p>	
<p>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</p>	<p>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</p>	<p>Acceptable</p>
<p>5. Impaired liver function. Estrogens may be poorly metabolized in patients with impaired liver function.-</p>	<p>5. Impaired liver function. Estrogens may be poorly metabolized in patients with impaired liver function.</p>	<p>Acceptable</p>
<p>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 <u>therapy who</u> are also <u>are also</u> <u>receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order</u></p>	<p>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</p>	<p>Acceptable</p>

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<p>to maintain their free thyroid hormone levels in an acceptable range.</p> <p>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.</p> <p>8. Exacerbation of endometriosis. Endometriosis may be exacerbated with administration of estrogen therapy.</p> <p>9. Hypocalcemia. Estrogens should be used with caution in individuals with severe hypocalcemia.</p>	<p>hormone levels in an acceptable range.</p> <p>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.</p> <p>8. Exacerbation of endometriosis. Endometriosis may be exacerbated with administration of estrogen therapy.</p> <p>9. Hypocalcemia. Estrogens should be used with caution in individuals with severe hypocalcemia.</p>	<p>Acceptable</p> <p>Acceptable</p> <p>Acceptable</p>
<p>B. [REDACTED] Patient Information See text of Patient Information after the HOW SUPPLIED section.</p>	<p>B. Patient Information See text of Patient Information after the HOW SUPPLIED section.</p>	<p>Acceptable</p>
<p>C. [REDACTED] 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</p>	<p>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</p>	<p>Acceptable</p>

<p>to hypogonadism, castration and primary ovarian failure.</p>	<p>primary ovarian failure.</p>	
<p>████████████████████ ██████████ ██████████; <u>Drug/Laboratory Test Interactions</u></p> <p>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.</p> <p>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.</p> <p>████████████████████ ██████████ ██████████ ██████████ ██████████ ██████████</p> <p>3. Other binding proteins may be elevated in serum, i.e.,</p>	<p>D. Drug/Laboratory Test Interactions</p> <p>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.</p> <p>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.</p> <p>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</p>	<p>Acceptable</p>

<p>F. ██████████-Pregnancy Category X Alora™ should not be used during pregnancy. See CONTRAINDICATIONS.</p>	<p>F. Pregnancy Category X Alora should not be used during pregnancy. See CONTRAINDICATIONS.</p>	<p>Acceptable</p>
<p>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.</p>	<p>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.</p>	<p>Acceptable</p>
<p>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</p>	<p>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</p>	<p>Acceptable</p>

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<p>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.</p>	<p>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.</p>	
<p>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.</p>	<p>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.</p>	<p>Acceptable</p>
<p>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</p>	<p>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</p>	

<p>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.</p> <p>See WARNINGS regarding induction of malignant neoplasms, thromboembolic disorders, gallbladder disease, and [REDACTED] hypercalcemia. See PRECAUTIONS regarding cardiovascular risk and elevated blood pressure.</p> <p>Incidence of adverse events > 2% of each treatment group is given in Table 4. [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>	<p>does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.</p> <p>See WARNINGS regarding induction of malignant neoplasms, thromboembolic disorders, gallbladder disease, and hypercalcemia. See PRECAUTIONS regarding cardiovascular risk and elevated blood pressure.</p> <p>Incidence of adverse events > 2% of each treatment group is given in Table 4.</p>	<p>Acceptable</p> <p>In footnote b to the table, remove the words '[REDACTED]' and add '[REDACTED]' from the sentence "Alora [REDACTED] were obtained from two 12-week studies of the treatment of menopausal symptoms."</p>
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<p>Table 4 Incidence of Adverse events >2% for Alora and Placebo Systems</p>	<p>Table 4 Incidence of Adverse events >2% for Alora and Placebo Systems</p>	<p>Superscript letters in referenced footnote</p>
<p>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.</p>	<p>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.</p>	<p>Acceptable</p>
<p>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</p>	<p>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</p>	<p>Acceptable</p>

NDA 20-655/S-008
 Label Review

<p>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.</p>	<p>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.</p>	
<p>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.</p> <p>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.</p> <p>In women who are not currently</p>	<p>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.</p> <p>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.</p> <p>In women who are not currently</p>	<p>Acceptable</p>

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 Label Review

<p>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 <u>one</u> week after withdrawal of oral therapy or sooner if menopausal symptoms reappear in less than one <u>one</u> week.</p>	<p>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.</p>	
<p>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 <u>Three</u> weeks of therapy followed by one <u>one</u> week without) for the treatment of postmenopausal symptoms. However, no studies have been conducted using this intermittent regimen for the prevention of postmenopausal osteoporosis.</p>	<p>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.</p>	<p>Acceptable</p>
<p>How supplied</p>	<p>How supplied</p>	<p>Acceptable</p>

Patient Package Insert

		<p><u>Alora Is Used In The Following Ways:</u> • To reduce moderate or severe menopausal symptoms. Change the last sentence to read as follows: <u>Most women do not need estrogen replacement</u></p>
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<p>Step 5 Removing the patch</p> <p>For Best Results, [REDACTED] with Your Patch Program</p>	<p>Step 5 Removing the patch</p> <p>For Best Results, [REDACTED] with Your Patch Program</p>	<p><u>therapy for longer than six months for these symptoms.</u></p> <p>To help reduce your chances of getting osteoporosis (thin weak bones). The third sentence should be changed to read as follows: <u>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.</u></p> <p>Who Should Not Use Alora The following language should be used for the third bulleted item: <u>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.</u></p> <p>Change the word [REDACTED] to "Stay"</p>
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NDA 20-655/S-008
Label Review

Conclusions

The application is approved based on the agreed upon labeling text submitted from the sponsor on February 5, 2002, and the above revisions provided to the sponsor April 5, 2002 via secured e-mail and included in the April 5, 2002, Approval letter.

Dornette Spell-LeSane, NP-C, MHA
Consumer Safety Officer

Phill Price, M.D.
Medical Officer

Shelley Slaughter, M.D., Ph.D.
Team Leader

Drafted: Spell-LeSane, 3.4.02
Finalized: Spell-LeSane, 4.5.02

CSO LABELING REVIEW

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/s/

Dornette Spell-LeSane
4/5/02 03:28:37 PM
CSO

Phill H. Price
4/5/02 03:59:32 PM
MEDICAL OFFICER
I concur.

Shelley Slaughter
4/5/02 04:03:22 PM
MEDICAL OFFICER
I concur.

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Division of Reproductive and Urologic Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-655/S-008

Name of Drug: Alora (estradiol transdermal system) 0.025, 0.05, 0.075 and 0.1 mg/day

Sponsor: Watson Laboratories, Inc.

Material Reviewed:

1. Physician Insert
2. Patient Package Insert
3. Draft Backing Film, Pouch and Carton labeling
4. DDMAC review (dated November 7, 2001)

Submission Date(s): June 12, 2001

Receipt Date(s): June 13, 2001

Background and Summary

This supplement was submitted to the Division in concurrence with NDA 21-310, submitted to the Division of Metabolic and Endocrine drug Products on January 12, 2001. The NDA provides for the addition of a new indication, prevention of postmenopausal osteoporosis, and a new strength, 0.025 mg/day. A labeling supplement was submitted to the Division of Reproductive and Urologic Drug Products on June 12, 2001, to the parent NDA 20-655 to revise the physician insert and the patient package insert to reflect the above changes.

Review

Revisions have been incorporated directly into the physician labeling and the patient package insert (attached). Additions have been noted with underlining, deletions have been noted as ~~strikeouts~~. Additional comments requiring response are in **14 pt bold face type**.

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Conclusions

Substantial changes were made to this label to bring in agreement with the following:

- a. Class labeling for HRT drug products
- b. the current Division's thinking regarding restructuring labeling to eliminate superfluous language
- c. recommendations from the Division of Metabolic and Endocrine Drug Products to include language related to the osteoporosis indication
- d. recommendations from the Division of Drug Marketing, Advertising, and Communications to revise the Patient Information sections to create a plain language document

This supplement is approvable pending final draft labeling.

Attachments:

Revised Physician Insert

Revised Patient Information Insert

Domette Spell-LeSane, NP-C
Regulatory Project Manager

Supervisory Comment/Concurrence:

Terri Rumble, BSN
Chief, Project Management Staff

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NDA 20-655 S/008

Drafted: November 14, 2001

Revised/Initialed:

Finalized:

Filename: NDA20655/s008csorev.doc

CSO LABELING REVIEW

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NDA 20-655/S-008

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

Dear Dorothy Frank:

We acknowledge receipt on February 6, 2002, of your February 5, 2002, resubmission to your supplemental new drug application for Alora® (estradiol transdermal system) 0.05, 0.075, and 0.1 mg/day.

This resubmission contains: (1) additional labeling revisions (2) efficacy data to support Table 3 regarding frequency of moderate to severe vasomotor symptoms, and (3) a graph for Figure 3 representing "Mean % change in BMD" in response to our January 18, 2002, action letter.

With this amendment, we have received a complete response to our January 18, 2002, action letter.

If you have any questions, call Dornette Spell-LeSane, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Terri Rumble, BSN
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jeanine Best
2/14/02 08:33:06 AM
signing for Terri Rumble

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NDA 20-655/S-008

PRIOR APPROVAL SUPPLEMENT

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

Dear Ms. Frank:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Alora ® (estradiol transdermal system) 0.05, 0.075, and 0.1 mg/day.

NDA Number: 20-655

Supplement Number: SLR-008

Date of Supplement: June 12, 2001

Date of Receipt: June 13, 2001

This supplement proposes the following changes: addition of a new indication, prevention of postmenopausal osteoporosis, and a new strength, 0.025 mg/day.

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 August 13, 2001, in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-655/S-008

Page 2

If you have any questions, call me at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Domette Spell-LeSane, NP-C
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Dornette Spell-LeSane
6/23/01 12:01:41 PM

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