CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-655/S-008

MEDICAL REVIEW

Medical Officer Summary of NDA Supplement

1. NDA 20-655 SLR008 Submission Date: June 12, 2001
M.O. Review Review Completed: November 15, 2001

Drug: Estradiol transdermal system

Generic Name: 17-Beta estradiol

Trade name: Alora®

Chemical Name: Estradiol USP (estra-1,3,5, (10)-triene-3, 17β

Sponsor: Watson Laboratories
Research Park, 417 Wakara Way
Salt Lake City, Utah 84108

Pharmacologic Category: Estrogen

Clinical Indication: Estrogen Replacement Therapy

Dosages and Route of Administration: 0.025mg per day, 0.05 mg per day, 0.075 mg per day, and 0.1 mg per day

NDA Drug Class: 3S

Related Drugs: Approved estradiol transdermal patches are Estraderm®, Climara®, Vivellle®,Menorest®, Alora® and Esclim®.

Summary/Issues

The sponsor currently has approval of Alora® for the treatment of moderate-to-severe vasomotor symptoms at the 0.05mg, the 0.075mg and 0.1mg per day doses of Alora® transdermal patches. The sponsor instituted a two-year placebo controlled trial for the prevention of osteoporosis. The Division of Metabolic and Endocrine Drug Products (DMEDP) reviewed this indication and their recommendation is for approval of the 0.025 mg/day, 0.05 mg/day and 0.075 mg/day doses for the prevention of postmenopausal osteoporosis.

Watson submitted draft labeling and has updated their label to be consistent with the Draft Labeling Guidance for Estrogen and Estrogen/Progestin Products of 1995 (Estrogen Class Labeling Guidance). Substantial changes have been made by the Agency to most sections of the submitted draft label. I will discuss in detail the most significant of these changes:

The **Box Warning** has been updated and the two paragraphs under # 2 have been moved to the Precautions section of the label.

Under **Clinical Pharmacology** seven paragraphs have been deleted and three paragraphs from the Estrogen Class Labeling Guidance have been inserted. A fourth paragraph is inserted describing estrogen effect upon bone resorption and disposition.

In the **Pharmacokinetic** section the sponsor's figure 1 has been deleted and all supportive text to figure 1 has been deleted since it refers to a comparison to Estraderm®, an alcohol reservoir patch, and Alora® which is a matrix patch. The distribution, excretion and metabolism sections are revised and the sponsor table 3 has been deleted. The sponsor will be asked to supply all data presently available relating to (Alora) patch adhesion reported in their clinical trials.

A Special populations section has been added with the following text: "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 on other special population, including patients with renal or hepatic impairment".

Under **Adhesion**, the sponsor was instructed to supply information regarding the new matrix formulation with appropriate language to support the adhesion data.

Under **Clinical Studies**

The term controlled clinical studies is removed. The sponsor's table 4 and all supportive text have been deleted. This table referred to a clinical trial with Alora compared to conjugated estrogens. This trial was never designed as a superiority trial and thus is not appropriate for estrogen class labels. The sponsor's table 5 is to be revised to present mean change from baseline rather than mean *percent* reduction from baseline of moderate to severe vasomotor symptoms.

HFD-510 will insert an appropriately modified (from the sponsor's draft) text and graph in this section.

Under **CONTRAINDICATIONS** no revisions in this section except after #1 Known or suspected pregnancy, the language "(see **PRECAUTIONS**)" has been added.

Under **WARNINGS**, this section has been significantly updated and renumbered and the following text inserted:

Induction of malignant neoplasms.

1a. **Endometrial cancer.** The reported endometrial cancer risk among unopposed estrogen users [redacted] 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 10 years or more, and this risk has been shown to persist for at least 8-15 years after estrogen therapy is discontinued.

1. **Breast Cancer.** While some epidemiological 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 24-40%), although this is based solely on epidemiological 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 healthcare 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 2-3 cases per 10,000 women per year.

Cerebrovascular disease. Embolic cerebrovascular events have been reported in women receiving [redacted] 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 women receiving [redacted] estrogen has been reported.

[redacted]

The **PRECAUTIONS** section is significantly updated and clinical conditions in this section are renumbered. Numbers 1,2 and 3 are modified and this section now includes a modified Carcinogenesis, Mutagenesis, and Impairment of Fertility section, Pregnancy Category X, a section on Nursing Mothers, a Pediatric Use section, and a section on Geriatric Use. The following is the recommended new language:

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 lower 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 [redacted] adverse effects on lipoprotein metabolism (e.g., lowering HDL and raising LDL) and [redacted] 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 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.

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.

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. [redacted]

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.

E. **Carcinogenesis, Mutagenesis, [redacted] Impairment of Fertility**. [redacted] 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.

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. Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. [redacted] is 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** section.

I. **Geriatric Use.** [redacted]

Under **ADVERSE REACTIONS**, the following introductory paragraph is inserted;

Because clinical trials are conducted under widely varying conditions, adverse reaction 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.

In this section the label should refer back to see **WARNINGS** regarding induction of malignant neoplasms, thromboembolic disorders, gallbladder disease, and hypercalcemia; See **PRECAUTIONS** regarding cardiovascular risk and elevated blood pressure.

The sponsor had been instructed to insert an adverse event table by Body System with clinical data originating in Alora® studies. Adverse events are to be reported which are ($\geq$ 2%).

The sponsor paragraph entitled "Vaginal bleeding" has been deleted; data from this paragraph may be inserted into the Adverse event table.

The section that reports "additional adverse reactions that have been reported with estrogen therapy" has been deleted since most of these AEs are more consistent with older oral contraceptive data. The two paragraphs reporting skin irritation have been deleted and this data should be incorporated into the Aes table. Previously, under the Pharmacokinetic section, data was requested that report the amounts of adhesion of the Alora® patch and how many of these patches fell off during clinical trials.

Under **DOSAGE AND ADMINISTRATION**

Under **Initiation of Therapy**, the paragraph that describes the treatment of moderate-to-severe vasomotor symptoms is appropriate.

HFD-510 has modified this paragraph that describes the prevention (not management) of osteoporosis.

Patient Package Insert

The patient package insert was substantially revised to fit a plain language format that has been introduced into more recently approved labels for estrogen products.

Recommendation:

The application is approvable pending submission by the sponsor of the recommended revised labeling changes to the Division of Reproductive and Urologic Drug Products (DRUDP) and DMEDP.

Phill H. Price, M.D.

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

/s/

Phill H. Price
11/16/01 02:02:14 PM
MEDICAL OFFICER

Shelley Slaughter
11/16/01 02:05:31 PM
MEDICAL OFFICER
I concur with the SLR review by Dr. Price

39 pages redacted from this section of the approval package consisted of draft labeling

NDA 20-655- S/008	ALORA
Document Date:	**November 19, 2001**

FDA Revisions From The November 16, 2001 Approvable Letter	**Sponsor Revisions Response To 11/16/02 Approvable Letter**	**Medical Officer Comments and Revisions**
ALORA® [redacted]	**Alora®** [redacted]	[redacted] to "(estradiol transdermal system)"
Continuous Delivery for Twice Weekly Dosing	Continuous Delivery for Twice Weekly Dosing	
PRESCRIBING INFORMATION	**PRESCRIBING INFORMATION**	
[redacted] **ESTROGENS** [redacted] **INCREASE THE RISK OF ENDOMETRIAL** [redacted] **CANCER.**	**ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER.**	[redacted] **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 [redacted] results in a [redacted]	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.	The sponsor made appropriate changes to the language in the **BOXED WARNING**

[redacted]

different endometrial risk profile than synthetic estrogens of equivalent estrogen dose.

DESCRIPTION

[redacted] is designed to deliver [redacted]-estradiol continuously and consistently over a 3 or 4-day interval upon application to intact skin. [redacted] Four strengths of **Alora** [redacted] 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** [redacted] contact surface areas of 9, 18, 27, and 36 cm^2 and [redacted], 0.75, 1.5, 2.3, and 3.0 mg of estradiol, USP, respectively. The composition of the systems per unit active surface is identical. Estradiol, USP [redacted] 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 [redacted] 272.39. The structural formula is:

DESCRIPTION

[redacted] is designed to deliver [redacted]-estradiol continuously and consistently over a 3 or 4-day interval upon application to intact skin. Four strengths of **Alora** [redacted] 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** [redacted] contact surface areas of 9, 18, 27, and 36 cm^2 and [redacted] 0.75, 1.5, 2.3, and 3.0 mg of estradiol, USP, respectively. The composition of the [redacted] per unit active surface is identical. Estradiol, USP is a white, crystalline powder [redacted]

In the first sentence **DESCRIPTION** section change [redacted] to "Alora® (estradiol transdermal system)" Delete the dash (-) preceding estradiol

[redacted] "Alora has contact surface areas"

Change "The composition of the

	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:	systems per unit active surface is identical" to "The composition of the estradiol transdermal system per unit area is identical"
Description section continued: The **Alora** [redacted] 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	Description section continued: The **Alora** [redacted] 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	**DESCRIPTION** section continued: Delete [redacted] from the following sentence. [redacted] **Alora** [redacted] consists of three layers.
CLINICAL PHARMACOLOGY [redacted] [redacted] Estrogens are [redacted] 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 [redacted]	**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	**CLINICAL PHARMACOLOGY** The sponsor made appropriate change to the introductory language. No additional changes during resubmission.

[redacted] estriol, at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to [redacted] 500 µg of estradiol daily, depending on the phase of the menstrual cycle. [redacted] After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone [redacted] and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.	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.	

postmenopausal [redacted] women.

[redacted]

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. [redacted] To date, two estrogen [redacted]

[redacted] receptors have been [redacted]

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

[redacted]

1 pages redacted from this section of the approval package consisted of draft labeling

[redacted]

mechanism [redacted] estrogen replacement therapy [redacted]

[redacted] acts to reduce the elevated levels of these hormones seen in postmenopausal [redacted] women.

Pharmacokinetics

[redacted] The skin metabolizes estradiol only to a small extent. In contrast, orally administered estradiol [redacted] is rapidly metabolized by the liver to estrone and its conjugates, giving rise to higher circulating levels

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 [redacted] 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** systems, respectively. [redacted]	**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	Sponsor made appropriate changes to the language under **Pharmacokinetics**; no additional changes required ***Absorption*** Change font to italics on this subheading.

[redacted]	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** : [redacted], respectively.	[redacted]
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	In another study, 20 women also were treated with three consecutive doses of **Alora**	The Sponsor's changes are acceptable for paragraph 3 in the ***Absorption*** section.

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.	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.	
[redacted]		
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 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 [redacted] trial in the prevention of postmenopausal osteoporosis of 2 year duration (Study 3). Table 2 provides a summary of these data.	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 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.	
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	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	
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 for the 0.025 mg/day dose, 35.9 pg/ml for the 0.05 mg/day dose and 50.1 pg/ml for the 0.075 mg/day dose. These values were linearly related and dose proportional.	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 for the 0.025 mg/day dose, 35.9 pg/ml for the 0.05 mg/day dose and 50.1 pg/ml for the 0.075 mg/day dose. These values were linearly related and dose proportional.	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.
Distribution No specific investigation of the tissue distribution of estradiol absorbed from **Alora** in humans has been conducted. [redacted] 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]	**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]	***Distribution*** Change font to italics for this subheading. The Sponsor made the appropriate changes to this section.

[redacted] **Metabolism** [redacted]	hormone binding globulin (SHBG) and [redacted] albumin. **Metabolism**	***Metabolism*** Change font to italics for this subheading.
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	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	The Sponsor's changes to the ***Metabolism*** section acceptable are acceptable

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.	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 [redacted] 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.	**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.	*Excretion* Change font to italics for this subheading.
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.	**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.	**Special Populations** The Sponsor's changes are acceptable

[redacted]

Adhesion
Comment: INFORMATION REGARDING THE NEW MATRIX FORMULATION HAS NOT BEEN PROVIDED. PLEASE SUBMIT APPROPRIATE LANGUAGE TO SUPPORT THE DATA.

[redacted]

Adhesion

[redacted] was evaluated in a randomized clinical trial involving 408 healthy postmenopausal women [redacted]

[redacted]

[redacted]

Adhesion
The Sponsor's language is not acceptable, the following language should be inserted:
"The adhesion potential of Alora was evaluated in a randomized [redacted] involving 408 healthy postmenopausal women who wore placebo systems corresponding to the 18 cm^2 size . Alora. The placebos were applied twice weekly for four 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 applications 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."

[redacted] **CLINICAL STUDIES**	**CLINICAL STUDIES**	Delete the word [redacted] from the subheading **CLINICAL STUDIES**
[redacted]	[redacted]	Change the heading [redacted] to "*Effects on Vasomotor Symptoms*"
Efficacy [redacted] of **Alora** has been studied in a double blind/double dummy, randomized, parallel [redacted] group, placebo-controlled trialinvolving a total of 268 postmenopausal women over a 12-week dosing period.	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.	
[redacted] Only women having estradiol and FSH serum concentrations in the postmenopausal range and who exhibited a weekly average of at least 60 moderate-to-[redacted]severe hot flushes during the screening period were enrolled in the studies.	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.	
[redacted]	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	

[redacted]	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)	**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. The acceptability of this language is pending confirmation of data in the table and its statistical significance.
Comment: SPONSOR NEEDS TO PRESENT MEAN CHANGE FROM BASELINE AT WEEKS 4, 8 AND 12 FOR THE 0.05 MG/DAY AND 0.1 MG/DAY ALORA AND PLACEBO TREATMENT GROUPS IN A TABLE AND RESUBMIT DATA.	Mean change from baseline table submitted	The sponsor did not submit data to support the mean change from baseline data presented in the table 3. Therefore, the table regarding VMS cannot be verified. The sponsor should submit the efficacy data in SAS transport format. 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. This is an approvable issue
Alora 0.05 mg/day and [redacted] 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. [redacted]		

[redacted] 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) [redacted]		
[redacted], vaginal cytology was obtained pre-dosing and at last visit in a total of [redacted] women treated with **Alora** 0.05 mg/day, in [redacted] women treated with **Alora** 0.1 mg/day and in 46 women in the placebo group. Superficial cells increased by a mean of [redacted] 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. [redacted] Lumbar spine bone mineral	[redacted] vaginal cytology was obtained pre-dosing and at last visit in [redacted] women treated with **Alora** 0.05 mg/day, in [redacted] women treated with **Alora** 0.1 mg/day and in 46 women in the placebo group. Superficial cells increased by a mean of [redacted], 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. [redacted] e	Add subheading "*Effects on vulvar and vaginal atrophy*" [redacted] Vaginal cytology was obtained pre-dosing and at last visit in a total of [redacted] 54 women treated with **Alora** 0.05 mg/day, in [redacted] 45 women treated with **Alora** 0.1 mg/day and in 46 women in the placebo group. Superficial cells increased by a mean of [redacted] 18.7%, [redacted] 23.7% and [redacted] 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. Change the heading [redacted]

density (BMD) was measured by DEXA in a two-year, randomized, multi-center, double-blind, [redacted] placebo-controlled, [redacted] study in [redacted] 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 (range 26 to 69), and the average number of years [redacted] 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 [redacted] 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 [redacted]	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 (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	[redacted] ' to "***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.

Comment: The patient population used for this graph is not clear. Again, the primary efficacy endpoint is at 2 years. A line graph using 'completer' data at one and 2 year time points would be more appropriate. There should also be separated data points using data from the intent to treat population, last observation carried forward. A paragraph describing effect sizes and sample sizes should be included with the proposed graph.	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 A total of [redacted] patients were included in the completer population compared with [redacted] patients in the intent-to-treat, last observation carried forward population. [redacted]	Language for figure 3 heading is acceptable The graph for figure 3 is not acceptable. The FDA's graph is a representative of the graph requested from the sponsor. However, the numbers of subjects used to generate the graph are not correct. A new graph should be generated using the correct numbers of subjects in the completer and ITT populations A total of [redacted]196 patients were included in the completer population compared with [redacted]258 patients in the intent-to-treat, last observation carried forward population. Delete the following sentences [redacted] Replace with: 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, 0.050 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. [redacted] Treatment of moderate-to-severe vasomotor symptoms associated with the menopause. [redacted] 2. [redacted] Treatment of vulvar and vaginal atrophy. 3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. 4. [redacted] Prevention of postmenopausal osteoporosis [redacted] 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]	**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 ([redacted] 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]	**INDICATIONS AND USAGE** section, the language in numbers 1 through 3 is acceptable Replace the text in #4 with the following: 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/d 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

dietary calcium intake).	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.	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 [redacted] 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. [redacted] 6. Known hypersensitivity to any of the components of **Alora**.	**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. [redacted] 6. Known hypersensitivity to any of the components of **Alora**.	**CONTRAINDICATIONS** Delete the parenthesis around see **PRECAUTIONS** Delete the semicolon following **PRECAUTIONS** and replace with a period. Delete period following pregnant woman and replace with a semicolon. Change #5 to "Active deep vein thrombosis/pulmonary embolism or history of these conditions
WARNINGS 1. [redacted] **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	**WARNINGS** 1. **Induction of malignant neoplasms.** a. **Endometrial cancer**. The reported endometrial cancer risk among	**WARNINGS** 1. INDUCTION OF MALIGNANT NEOPLASMS. **Endometrial cancer**. Change font to italics

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 [redacted] more, and this risk has been shown to persist for at least 8-15years after estrogen therapy is discontinued..	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 8-15years after estrogen therapy is discontinued..	Change "[redacted]" to "8 to15 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 24-40%), although this is based solely on epidemiologic studies, and definitive conclusions await prospective, controlled clinical trials. Women without a uterus who require hormone replacement	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	***Breast cancer*** Change font to italics

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.	significantly (by about 24-40%), 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	o 24% to 40%,

	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.	**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.	**Change "Thrombolic disorders" to "Thrombolic Disorders"**
Venous thromboembolism. Several epidemiologic studies have found an increased risk of venous	**Venous thromboembolism.** Several epidemiologic studies have found an	***Venous thromboembolism*** **Change font to italics**

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 2-3 cases per 10,000 women per year.	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 [redacted] cases per 10,000 women per year.	Change the risk in current ERT users was increased to [redacted] cases to "2 to 3" cases per 10,000 women per year.
Cerebrovascular disease. Embolic cerebrovascular events have been reported in women receiving [redacted] estrogens.	**Cerebrovascular disease.** Embolic cerebrovascular events have been reported in women receiving [redacted] estrogens.	**Cerebrovascular disease** Change font to italics. change statement to read "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,	**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	***Cardiovascular disease*** Change font to italics.

pulmonary embolism, and thrombophlebitis.	prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.	
3. —**Gallbladder disease.** [redacted] a 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving [redacted] estrogen [redacted]	3. **Gallbladder disease.** [redacted] 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving [redacted] estrogen [redacted]	**Change heading to "Gallbladder Ddisease."** Replace text with " A 2 to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported

[redacted] 4. [redacted]-**Hypercalcemia.** [redacted] 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.	4. **Hypercalcemia.** [redacted] 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.	**Hypercalcemia.** Change [redacted].1" to "Estrogen administration"
PRECAUTIONS **A. GENERAL** 1. [redacted] -**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. [redacted]	**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. There are, however, possible risks that may be associated with the use of progestins in	**PRECAUTIONS**, change subheading font from ' [redacted] to **General** **Change subheading font to italics** *Addition of a progestin when a woman has not had a hysterectomy.*

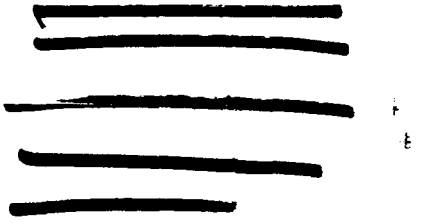
There are, however, possible risks that may be associated with the use of progestins in estrogen replacement regimens. These include: adverse effects on lipoprotein metabolism (e.g., lowering HDL and raising LDL) and impairment of glucose tolerance. The choice of progestin, its dose, and its regimen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

(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.	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.	
[redacted]		
Elevated blood pressure. In a small number of case reports, substantial increases in blood pressure during estrogen replacement therapy [redacted] 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.	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.	***Elevated blood pressure*** Change subheading font to italics
[redacted]		

[redacted]		
4. **Familial hyperlipoproteinemia.** In patients with familial defects of lioprotein metabolism, estrogen [redacted] therapy may be associated with [redacted] elevations of plasma triglycerides leading to pancreatitis and other [redacted] complications.	4. **Familial hyperlipoproteinemia.** In patients with familial defects of lioprotein metabolism, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications	***Familial hyperproteinemia*** Change subheading font to italics
5. **Impaired liver function.** Estrogens may be poorly metabolized in patients with impaired liver function.	5. **Impaired liver function.** Estrogens may be poorly metabolized in patients with impaired liver function..	***Impaired liver function*** Change subheading font to italics
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, however, may require increased doses in order to maintain their free thyroid hormone levels in an acceptable range.	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, [redacted]	***Hypothyroidism.*** Change subheading font to italics Change text to read, "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." [redacted]

		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.	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	***Fluid retention*** Change subheading font to italics
Exacerbation of endometriosis. Endometriosis may be exacerbated with administration of estrogen therapy. 9. **Hypocalcemia**. Estrogens should be used with caution in individuals	8. **Exacerbation of endometriosis**. Endometriosis may be exacerbated with administration of estrogen therapy.	***Exacerbation of endometriosis*** Change subheading font to italics

with severe hypocalcemia. **B. PATIENT INFORMATION** See text of Patient Information after the **HOW SUPPLIED** section. C. [redacted]**–LABORATORY TESTS** Estrogen administration should[redacted] be guided by clinical response at the[redacted] –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. [redacted]~~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	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	***Hypocalcemia*** Change subheading font to italics **C. Laboratory Tests** Subheading should be bolded Remove space before "Estrogen" at the beginning of the sentence **D. DRUG/LABORATORY TEST INTERACTIONS.** Subheading should be bolded

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	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	

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.	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,	**E. CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY** Long-term continuous administration of natural and synthetic estrogens	**E. CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY** Last sentence should read "See **CONTRAINDICATIONS.**" Parenthesis should be removed and Warnings should be remove from the text.

and liver. [redacted] See CONTRAINDICATIONS [redacted]	in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. (See CONTRAINDICATIONS [redacted]	
F. **PREGNANCY Category X** [redacted] Alora™ should not be used during [redacted] pregnancy. See CONTRAINDICATIONS.	**F. PREGNANCY Category X** Alora™ should not be used during pregnancy. See CONTRAINDICATIONS.	**F.** Subheading should be bolded
G. **NURSING MOTHERS** [redacted] 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.	**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.	**G, Nursing mothers** No change
[redacted] H. [redacted] **PEDIATRIC USE.** Estrogen replacement therapy has been used for the induction of puberty in adolescents with some forms of pubertal delay. Safety and [redacted]	**H. PEDIATRIC USE.** Estrogen replacement therapy has been used for the induction of puberty in adolescents [redacted]	**H. Pediatric Use** Subheading should be bolded.

effectiveness in [redacted] 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)	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)	Delete the parenthesis (See **INDICATIONS** and **DOSAGE AND ADMINISTRATION** sections)	
I. GERIATRIC USE	**I. GERIATRIC USE**	The subheading should be bolded.	
Comment: Watson should refer to	Clinical studies of **Alora** did	The geriatric statement is acceptable	

CRF§201.57(f)(10) for appropriate language.	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 [redacted]	**ADVERSE REACTIONS**	Adverse Reaction table is acceptable however, The notations in the table and the footer should be changed as follows: [a]Adverse events for the three lower Alora doses and placebo were obtained from the two year prevention osteoporosis study for column 1-4 [b] Adverse events for the highest Alora dose were obtained from the two [redacted] 12-week studies of the treatment of menopausal symptoms [redacted] [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)

[redacted]

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.

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.

[redacted]

-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 > [redacted] 2% of each treatment group is given in Table [redacted]

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

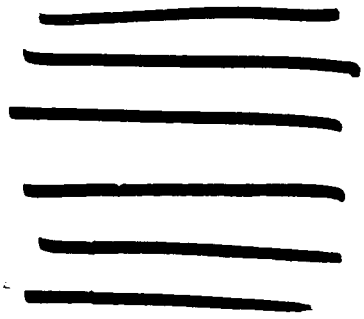
Incidence of adverse events > 2% of each treatment group is given in Table 4.

[redacted]

	the highest Alora dose were obtained from the two [redacted] 12-week treatment of menopausal symptom [redacted]	

APPEARS THIS WAY
ON ORIGINAL

2 pages redacted from this section of the approval package consisted of draft labeling

		
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.	**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.	**OVERDOSAGE** No change
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.	**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	**DOSAGE AND ADMINISTRATION** No change

In the event that a system should fall off, the same system may be reapplied. If necessary, a new system may be [redacted] applied to another site. The original treatment schedule should be maintained. [redacted]	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 [redacted]	**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	**Initiation of Therapy** Change Arabic numeral [redacted] to "one" in last paragraph

[redacted] For treatment of moderate-to-severe vasomotor symptoms, [redacted] 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 [redacted] of postmenopausal osteoporosis, [redacted] 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. [redacted] 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 [redacted] events. In women who are not currently taking oral estrogens or in women switching from topical therapy or another	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.	

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 1 week after withdrawal of oral therapy or sooner if menopausal symptoms reappear in less than 1 week.	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 1 week after withdrawal of oral therapy or sooner if menopausal symptoms reappear in less than 1 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. 3 weeks of therapy followed by 1 week [redacted] without) for the treatment of postmenopausal symptoms. However, no studies have been conducted using this intermittent regimen for the prevention of postmenopausal osteoporosis.	**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. 3 weeks of therapy followed by 1 week without) for the treatment of postmenopausal symptoms. However, no studies have been conducted using this intermittent regimen for the prevention of postmenopausal osteoporosis.	**Therapeutic Regimen** Change Arabic number "1" and "3" to one and three.

	HOW SUPPLIED	HOW SUPPLIED No change
[redacted] Patient Information [redacted] 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. [redacted] **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 [redacted] medicine, it is important to visit your [redacted] healthcareprovider regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your [redacted] healthcare provider should [redacted] check any unusual vaginal bleeding to find out the cause. Women who do not have a uterus have no risk of endometrial cancer.	**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	

[redacted]	who do not have a uterus have no risk of endometrial cancer.	[redacted] ..' to "Women who do not have a uterus have almost no risk of endometrial cancer".
What is Alora™ Alora is a patch that contains [redacted] estrogen hormone [redacted] -estradiol. When applied to the skin as directed below, the Alora™ patch releases estrogen through the skin in-to the abdomen.	**What is Alora™** Alora is a patch that contains [redacted] estrogen hormone [redacted] estradiol. When applied to the skin as directed below, the Alora™ patch releases estrogen through the skin into the abdomen.	**What is Alora™** Alora is a patch that contains [redacted] the estrogen hormone [redacted] estradiol.
Alora Is [redacted] -Used In The Following Ways: • **To reduce moderate or severe menopausal symptoms.** Estrogens are hormones made by [redacted] a women'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. [redacted] Tthe 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	***Alora Is Used In The Following Ways:*** • **To reduce moderate or severe menopausal symptoms.** Estrogens are hormones made by a women'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	Change text " [redacted] "woman's ovaries". "surgical menopause." Remove the period to inside the parenthesis

adjust to lower estrogen levels. [redacted] do not need estrogen replacement for longer than six months for these symptoms..	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. [redacted] need estrogen replacement for longer than six months for these symptoms. [redacted]	Last sentence has ' [redacted] remove the second period
• **To treat itching, burning, and dryness in and around the vagina** [redacted] ~~due~~ <u>due to</u> **menopause.**	• **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 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. Alora may be used as part of a program of weight-bearing exercise like walking and running <u>along with</u> ~~and~~ calcium supplements to reduce your chances of getting osteoporosis. Before you change your calcium intake or exercise habits, it is	• **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. [redacted]	**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. <u>Women who have menopause at an early age, are thin, smoke or have a family history of osteoporosis are more likely to develop osteoporosis.</u>

important to discuss these lifestyle changes with your healthcare provider to find out if they are safe for you.

[redacted]

Who Should Not Use Alora™

[redacted] Do not use Alora if you:

to reduce your chances of getting osteoporosis. Before you change your [redacted], it is important to discuss these lifestyle changes with your healthcare provider to find out if they are safe for you.

[redacted]

Who Should Not Use Alora™

Do not use Alora if you
• .

[redacted] Before you change your [redacted] 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 osteopirosis. 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.

[redacted]

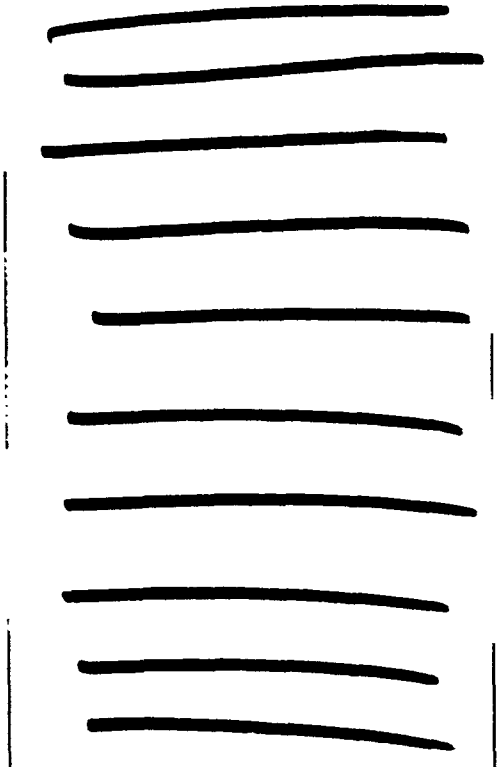
[redacted] **think you may be pregnant,** [redacted]. Using Alora™ while you are pregnant may harm your unborn child. Do not use Alora to prevent miscarriage.	**think you may be pregnant**,. Using Alora™ while you are pregnant may harm your unborn child. Do not use Alora to prevent miscarriage.	
• [redacted] **have unusual vaginal bleeding.** [redacted] If you [redacted] develop vaginal bleeding while using Alora talk with your healtcare provider [redacted] about proper treatment [redacted]	• **have unusual vaginal bleeding.** If you develop vaginal bleeding while using Alora talk with your healtcare provider about proper treatment	
• [redacted] **have had certain cancers.** Estrogens may increase the risk of certain types of cancer, including cancer of the breast or uterus. If you have had cancer, talk to your healthcare provider about the use of Alora™.	• **have had certain cancers.** Estrogens may increase the risk of certain types of cancer, including cancer of the breast or uterus. If you have had cancer, talk to your healthcare provider about the use of Alora™.	**have had certain cancers** If you have or have had cancer, talk to your healthcare provider about the use of Alora™.
• [redacted] **have** [redacted] **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. [redacted]	• **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.	
• [redacted] have recently had a baby.	• **have recently had a baby.** Do not use Alora™ to	

Do not use Alora™ to stop your breasts from filling with milk after a baby is born. [redacted]	stop your breasts from filling with milk after a baby is born.	
• [redacted] are allergic to Alora or any of the ingredients in it.	• **are allergic to Alora or any of the ingredients in it.**	
What Are The Possible Risks And Side Efects Of Alora™	**What Are The Possible Risks And Side Effects Of Alora** [redacted]	
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.	**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.	Remove trademark symbol from Alora
Less common but serious effects include: • Cancer of the uterus. • Cancer of the breast • Gallbladder disease • Abnormal blood clotting	**Less common but serious effects include:** • Cancer of the uterus. • Cancer of the breast • Gallbladder disease • Abnormal blood clotting	Add periods to end of bulleted sentences. Add the the following heading and text after Less common but serious

		side effects **"These are some of the warning signs of serious side 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.	**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.	Change **"What Can I Do To Lower My Chances Of Getting A Serious Side Effect With Alora?"** To **"What Can I Do to Lower My Chances of Getting a Serious Side Effect With Alora?"**
How should I use Alora [redacted]	**How should I use Alora™**	**How should I use Alora** The Sponsor has made the appropriate changes

[redacted] **Before you begin, read all the information in these 5 steps.** **Step 1. Choose [redacted] 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.**	**Before you begin, read all the information in these 5 steps.** **Step 1. Choose [redacted] 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.**	changes	
[redacted] For example, if you apply your first patch on Sunday, take that patch off on Wednesday and put on a new one. [redacted] Stay on this schedule as long as you use **Alora**. To help remind [redacted] 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.	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.	**Step 2 Before you apply the patch** • Make sure the skin at the spot is: • •Freshly washed, but **dry and cool** (wait a		

• 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.**	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.**		
• As you [redacted] get use 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. [redacted]	• As you get use 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.	**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.	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.**	• **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. [redacted] • • • **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.	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.	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.	**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 [redacted] healthcare provider.	**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, [redacted] 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;	**For Best Results, [redacted] 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;	
- Linking the days you change your patch to other things that always	- Linking the days you change your patch to	-

happen on those days (e.g., an exercise class, meetings, etc.)	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. [redacted] - If the patch starts to lift, simply press it back in place.	• **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 [redacted] 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.**	• **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?	**How should I store Alora?**	No change	

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

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Project Manager

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Medical Officer

Shelley Slaughter, M.D., Ph.D
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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/

Dornette Spell-LeSane
1/18/02 05:08:09 PM
CSO

Phill H. Price
1/18/02 05:11:51 PM
MEDICAL OFFICER
I concur

Shelley Slaughter
1/18/02 05:16:33 PM
MEDICAL OFFICER
I concur

20 pages redacted from this section of the approval package consisted of draft labeling