

ANDA 86-715/S-030 (0.3 mg)
83-209/S-054 (0.625 mg)

MAR 10 1998

Solvay Pharmaceuticals, Inc.
Attention: J. Greg Perkins, Ph.D.
901 Sawyer Road
Marietta, GA 30062

Dear Sir:

This is in reference to your supplemental new drug applications dated March 29, 1996, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug applications for ESTRATAB® (Esterified Estrogens Tablets, USP).

Reference is also made to your amendments and correspondence dated January 16, February 10 (ANDA 86-715), March 21, May 6, July 31, August 6, 1997 and March 2, 1998.

The supplemental applications provide for revised package insert labeling to include an additional indication for the prevention of osteoporosis in postmenopausal women.

We have completed the review of these supplemental applications and they are approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

*Final copy
not signed by woodcock
JMM 3/16/98*

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research



SOLVAY PHARMACEUTICALS

March 2, 1998

Mr. Douglas L. Sporn, Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

RECEIVED

Dear Mr. Sporn:

RE: **ESTRATAB[®] (Esterified Estrogens Tablets, USP)**
ANDA 86-715/S-030 (0.3 mg)
ANDA 83-209/S-054 (0.625 mg)

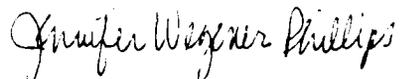
Reference is made to the supplemental applications listed above, submitted March 29, 1996, for the abbreviated new drug applications for ESTRATAB[®] (Esterified Estrogens Tablets, USP) 0.3 mg and 0.625 mg which provided for the addition of a prevention of osteoporosis indication. Reference is also made to a February 23, 1998 telephone conversation between Carol Holquist of the Office of Generic Drugs, and Dr. Greg Perkins, Dr. Jennifer Phillips, and Anisa Dhalla of Solvay Pharmaceuticals, Inc., during which you requested revised final printed labeling for these supplemental applications.

Final printed labeling for the physician insert (Attachment 1) and the patient insert (Attachment II) is included. This labeling includes the following revisions:

1. Information concerning the 1.25 mg strength has been deleted from the title information and the DESCRIPTION and HOW SUPPLIED sections of the labeling.
2. The statement "CAUTION: Federal law prohibits dispensing without prescription" has been revised to "Rx only" as required in the February 19, 1998 document "Guidance for Industry: Implementation of Section 126, Elimination of Certain Labeling Requirements of the Food and Drug Modernization Act of 1997".
3. Item 4 of the DOSAGE AND ADMINISTRATION section of the physician insert has been revised to read: "For prevention of osteoporosis—therapy with ESTRATAB[®] Tablets to prevent postmenopausal bone loss should be initiated as soon as possible after menopause. Therapy should be initiated at a daily dose of 0.3 mg and may be increased to a maximum daily dose of 1.25 mg if necessary to control concurrent menopausal symptoms." Revised wording was proposed during a February 25, 1998 telephone contact between Carol Holquist and Jennifer Phillips, and on March 2, 1998, Ms. Holquist indicated that the wording above would be acceptable.

Should you have any questions concerning this matter, please contact Anisa Dhalla,
Manager, Labeling and Submissions, at (770) 578-5931.

Sincerely,



Jennifer Wegener Phillips, Pharm.D.
Director, Regulatory Affairs

cc: Desk Copy to Carol Holquist, Office of Generic Drugs

PHYSICIAN LABELING ESTRATAB®

(Esterified Estrogens Tablets, USP)
0.3 mg, 0.625 mg, 2.5 mg

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN.

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 unexplained persistent or recurring abnormal vaginal bleeding. There is no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens of equal estrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

There is no indication for estrogen therapy during pregnancy or during the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of thrombosis or pulmonary embolism and are not indicated for the prevention of postpartum breast engorgement.

Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous-cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. The 1985 DES Task Force concluded that these DES analogs may be associated with a subsequent increased risk of breast cancer in the mothers, although a causal relationship is still unproven and the observed level of excess risk is similar to that for a number of other breast cancer risk factors.

DESCRIPTION

ESTRATAB® (Esterified Estrogens Tablets, USP) Each blue, sugarcoated tablet contains 0.3 mg. Each yellow, sugarcoated tablet contains 0.625 mg. Each light purple, sugarcoated tablet contains 2.5 mg.

ESTRATAB® Tablets for oral administration is a mixture of the sodium salts of the sulfate esters of the estrogen substances, principally estrone, that are prepared synthetically from plant steroid precursors. Esterified Estrogens, USP contain not less than 75.0 percent and not more than 85.0 percent of sodium estrone sulfate, and not less than 6.8 percent and not more than 15.0 percent of sodium equilin sulfate, in such proportion that the total of these two components is not less than 80.0 percent.

Inert ingredients: Acacia, calcium carbonate, carnauba wax, carbomethylcellulose sodium, citric acid, colloidal silicon dioxide, decylated monoglyceride, gelatin, anhydrous lactose, magnesium stearate, methylparaben, microcrystalline cellulose, pharmaceutical glaze, povidone, propylparaben, stearic acid, sodium benzoate, sodium bicarbonate, sorbic acid, sucrose, corn starch, titanium dioxide and triethyl citrate. The 0.3 mg tablet coating contains FD&C Blue #1 Lake; the 0.625 mg tablet coating contains D&C Yellow #10 Lake, FD&C Yellow #8 Lake and FD&C Blue #2 Lake; and the 2.5 mg tablet coating contains FD&C Red #40 Lake and FD&C Blue #2 Lake. In addition, the tablet imprinting ink for the 0.3 mg and 0.625 mg tablets contains black iron oxide, FD&C Blue #40 Lake, FD&C Red #40 Lake and FD&C Yellow #8 Lake. The 2.5 mg imprinting ink contains Soy lecithin, dimethyl polysiloxane, pharmaceutical shellac and titanium dioxide.

ACTIONS/CLINICAL PHARMACOLOGY

Estrogen drug products act by regulating the transcription of a limited number of genes. Estrogens diffuse through cell membranes, distribute themselves throughout the cell, and bind to and activate the nuclear estrogen receptor, a DNA-binding protein which is found in estrogen-responsive tissues. The activated estrogen receptor binds to specific DNA sequences, or hormone response elements, which enhance the transcription of selected genes and in turn lead to the observed effects. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, and bone of women.

Estrogens are important in the development and maintenance of the female reproductive system and are often characterized by dose response. By dose response, they cause growth and development of the uterus, Fallopian tubes, and vagina. With other hormones, such as pituitary hormones and progesterone, they cause enlargement of the breasts through promotion of ductal growth, stromal development, and the accretion of fat. Estrogens are directly involved with other hormones, especially progesterone, in the process of the endometrial menstrual cycle and pregnancy, and affect the release of pituitary gonadotropins. They also contribute to the shaping of the skeleton, maintenance of bone and elasticity of urogenital structures, changes in epiphyseal of the long bones that allow for the pubertal growth spurt and its termination, and pigmentation of the nipples and genitals.

Estrogens occur naturally in several forms. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 micrograms of estradiol daily, depending on the phase of the menstrual cycle. This is converted primarily to estrone, which naturally-occurring estrogens circulate in the blood largely bound to sex hormone-binding globulin and albumin, only unbound estrogens enter target tissue cells. A significant proportion of the circulating estrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogenic species. A certain proportion of the estrogens is secreted into the bile and then reabsorbed from the intestine. During this enterohepatic recirculation, estrogens are desulfated and reutilized and undergo degradation through conversion to less active estrogens (estrol and other estrogens), oxidation to nonestrogenic substances (catechol estrogens), which interact with catecholamine metabolism, especially in the central nervous system, and conjugation with glucuronic acids (which are then rapidly excreted in the urine).

Estrogens used in therapy are well absorbed through the skin, mucous membranes, and gastrointestinal tract. When applied for a local action, absorption is usually sufficient to cause systemic effects. When conjugated with aryl and alkyl groups for parenteral administration, the rate of absorption of oily preparations is slowed with a prolonged duration of action, such that a single intramuscular injection of estradiol valerate or estradiol cypionate is absorbed over several weeks.

Administered estrogens and their esters are handled within the body essentially the same as the endogenous hormones. Metabolic conversion of estrogens occurs primarily in the liver (first pass effect), but also at local target tissue sites. Complex metabolic processes result in a dynamic equilibrium of circulating conjugated and unconjugated estrogenic forms which are continually interconverted, especially between estrone and estradiol and between estradiol and non-estradiol forms. Although naturally-occurring estrogens circulate in the blood largely bound to sex hormone-binding globulin and albumin, only unbound estrogens enter target tissue cells. A significant proportion of the circulating estrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogenic species. A certain proportion of the estrogens is secreted into the bile and then reabsorbed from the intestine. During this enterohepatic recirculation, estrogens are desulfated and reutilized and undergo degradation through conversion to less active estrogens (estrol and other estrogens), oxidation to nonestrogenic substances (catechol estrogens), which interact with catecholamine metabolism, especially in the central nervous system, and conjugation with glucuronic acids (which are then rapidly excreted in the urine).

When given orally, naturally-occurring estrogens and their esters are extensively metabolized (first pass effect) and circulate primarily as estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogenic species. This results in limited oral potency. By contrast, synthetic estrogens, such as ethinyl estradiol and the nonsteroidal estrogens, are degraded very slowly in the liver and other tissues, which results in their high intrinsic potency. Estrogen drug products administered by non-oral routes are not subject to first-pass metabolism, but also undergo significant hepatic uptake, metabolism, and enterohepatic recycling.

Clinical Studies

A two-year, double-blind, placebo-controlled, randomized study was conducted in 406 postmenopausal women to determine the efficacy of continuously administered ESTRATAB® Tablets (0.3 mg, 0.625 mg, and 1.25 mg), unopposed by a progestin, on the prevention of postmenopausal osteoporosis. Efficacy was evaluated by semi-annual determination of lumbar spine (L1-L4) BMD and hip BMD changes (DXA). The results (see Tables 1, 2 and Figures 1, 2) of this study demonstrate that ESTRATAB® Tablets at doses of 0.3 mg, 0.625 mg, and 1.25 mg, is effective in the prevention of postmenopausal osteoporosis. Compared to placebo, patients treated with ESTRATAB® Tablets had significant increases in lumbar BMD and hip BMD.

Table 1. Mean Percent Change From Baseline in Lumbar Spine (L1-L4) BMD

Mean Percent Change in Lumbar Spine BMD	8 Mos	12 Mos	18 Mos	24 Mos
ESTRATAB® 0.3 mg	1.1	1.8	2.5	3.2
ESTRATAB® 0.625 mg	1.1	1.8	2.5	3.2
ESTRATAB® 1.25 mg	1.1	1.8	2.5	3.2
Placebo	-0.2	-0.5	-0.8	-1.1

5. Treatment of advanced estrogen-dependent carcinoma of the prostate (for palliation only).

6. Prevention of osteoporosis

Since estrogen administration is associated with risk as well as benefit, selection of patients should ideally be based on prospective identification of risk factors for developing osteoporosis. Unfortunately, there is no certain way to identify those women who will develop osteoporotic fractures. Most prospective studies of efficacy for this indication have been carried out in white menopausal women, without stratification by other risk factors, and tend to show a universally salutary effect on bone. Thus, patient selection must be individualized based on the balance of risks and benefits. A more favorable risk/benefit ratio exists in a hysterectomized woman because she has no risk of endometrial cancer (see Banned Warning).

Estrogen replacement therapy reduces bone resorption and retards or halts postmenopausal bone loss. Case-control studies have shown an approximately 90 percent reduction in hip and wrist fractures in women whose estrogen replacement was begun within a few years of menopause. Studies also suggest that estrogen reduces the rate of vertebral fractures. Even when started as late as 6 years after menopause, estrogen prevents further loss of bone mass for as long as the treatment is continued.

The results of a two-year, randomized, placebo-controlled, double-blind dose-ranging study have shown that daily continuous treatment with 0.3, 0.625, or 1.25 mg esterified estrogens prevents vertebral bone mass loss in postmenopausal women (See ACTIONS/CLINICAL PHARMACOLOGY). When estrogen therapy is discontinued, bone mass declines at a rate comparable to the immediate postmenopausal period. There is no evidence that estrogen replacement restores bone mass to premenopausal levels.

As skeletal maturity there are sex and race differences in both the total amount of bone present and its density, in favor of men and blacks. Thus, women have a higher peak bone mass because they start with less bone mass and, for several years following natural or induced menopause, the rate of mass decline is accelerated. White and Asian women are at higher risk than black women.

Early menopause is one of the strongest predictors for the development of osteoporosis. In addition, other factors affecting the skeleton which are associated with osteoporosis include genetic factors (small build, family history), endocrine factors (hypoparathyroidism, hyperparathyroidism, Cushing's syndrome, hyperparathyroidism, Type I diabetes), lifestyle factors (smoking, alcohol abuse, sedentary exercise habits) and nutrition (low average body weight, dietary calcium intake).

The mainstays of prevention and management of osteoporosis are estrogen, an adequate lifetime calcium intake, and exercise. 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. By comparison, premenopausal women require about 1000 mg/day and the average calcium intake in the USA is 400-600 mg/day. Therefore, when not contraindicated, calcium supplementation may be helpful.

Weight-bearing exercise and nutrition may be important adjuncts to the prevention and management of osteoporosis. Immobilization and prolonged bed rest produce rapid bone loss, while weight-bearing exercise has been shown both to reduce bone loss and to increase bone mass. The optimal type and amount of physical activity that would prevent osteoporosis have not been established. However, in two studies, an hour of walking and running exercises twice or three times weekly significantly increased lumbar spine bone mass.

CONTRAINDICATIONS

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

1. Known or suspected pregnancy (See Banned Warning). Estrogens may cause fetal harm when administered to a pregnant woman.
2. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease.
3. Known or suspected estrogen-dependent neoplasia.
4. Undiagnosed abnormal genital bleeding.
5. Active thrombophlebitis or thromboembolic disorders.

WARNINGS

Induction of malignant neoplasms

Endometrial Cancer: The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and increases 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. In three studies, persistence of risk was demonstrated for 8 to over 15 years after cessation of estrogen treatment. In one study a significant decrease in the incidence of endometrial cancer occurred six months after estrogen withdrawal. Concurrent progestin therapy may offset this risk but the overall health impact in postmenopausal women is not known (see PRECAUTIONS).

Breast Cancer: While the majority of studies have not shown an increased risk of breast cancer in women who have ever used estrogen replacement therapy, some have reported a moderately increased risk (relative risks of 1.3-2.0) in those taking higher doses or those taking lower doses for prolonged periods of time, especially in excess of 10 years. Other studies have not shown this relationship.

Congenital lesions with malignant potential: Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders, and possibly other birth defects. Studies of women who received DES during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. Although some of these changes are benign, others are precursors of malignancy.

2. Gallbladder disease
Two studies have reported a 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens.
3. 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. These risks cannot necessarily be extrapolated from men to women. However, to avoid the theoretical cardiovascular risk caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.
4. Elevated Blood Pressure
Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often blood pressure has remained the same or has dropped. One study showed that postmenopausal estrogen users have higher blood pressure than non-users. Two other studies showed slightly lower blood pressure among estrogen users compared to nonusers. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use.
5. Hypercalcemia
Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

PRECAUTIONS

General

1. **Adjuvant of a progestin:** Studies of the addition of a progestin for ten 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. Morphological and biochemical studies of endometria suggest that 10 to 14 days of progestin are needed to provide maximal maturation of the endometrium and to reduce the likelihood of hyperplastic changes.

There are, however, possible risks which may be associated with the use of progestin in estrogen replacement regimens. These include:

- (a) adverse effects on lipoprotein metabolism including HDL and LDL
- (b) possible increase in the risk of thromboembolic disease

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tion to less active estrogens (estrone and other estrogens), oxidation to nonsteroidal substances, catecholamines, which interact with catecholamine metabolism, especially in the central nervous system, and conjugation with glucuronic acids (which are then rapidly excreted in the urine).

When given orally, naturally-occurring estrogens and their esters are extensively metabolized (first pass effect) and circulate primarily as estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogenic species. The results in limited oral potency. By contrast, synthetic estrogens, such as ethinyl estradiol and the nonsteroidal estrogens, are degraded very slowly in the liver and other tissues, which results in their high intrinsic potency. Estrogen drug products administered by non-oral routes are not subject to first-pass metabolism, but also undergo significant hepatic uptake, metabolism, and enterohepatic recycling.

Clinical Studies

A two-year, double-blind, placebo-controlled, randomized study was conducted in 406 postmenopausal women to determine the efficacy of continuously administered ESTRATAB[®] Tablets (0.3 mg, 0.625 mg, and 1.25 mg), unopposed by a progestin, on the prevention of postmenopausal osteoporosis. Efficacy was evaluated by sequential determination of lumbar spine (L1-L4) BMD and hip BMD changes (DXA). The results (see Tables 1, 2 and Figures 1, 2) of this study demonstrate that ESTRATAB[®] Tablets, at doses of 0.3 mg, 0.625 mg, and 1.25 mg, is effective in the prevention of postmenopausal osteoporosis. Compared to placebo, patients treated with ESTRATAB[®] Tablets had significant increases in lumbar BMD and hip BMD.

Table 1. Mean Percent Change From Baseline in Lumbar Spine (L1-L4) BMD

	Mean Percent Change in Lumbar Spine BMD			
	6 Mos.	12 Mos.	18 Mos.	24 Mos.
Placebo	-2.76	-1.94*	-1.85*	-1.97*
ESTRATAB [®] 0.3 mg	0.81**	1.32**	1.47**	1.42**
ESTRATAB [®] 0.625 mg	1.32**	2.17**	2.13**	2.29**
ESTRATAB [®] 1.25 mg	2.38**	3.99**	4.11**	4.38**

* p<0.05 compared to baseline
* p<0.05 compared to placebo

Table 2. Mean Percent Change From Baseline in Hip BMD

	Mean Percent Change in Hip BMD			
	6 Mos.	12 Mos.	18 Mos.	24 Mos.
Placebo	-0.06	-0.48	-0.48	-0.82
ESTRATAB [®] 0.3 mg	1.09**	1.21**	1.71**	1.59**
ESTRATAB [®] 0.625 mg	0.73	1.71**	2.29**	2.78**
ESTRATAB [®] 1.25 mg	1.46**	1.55**	1.72**	2.06**

* p<0.05 compared to baseline
* p<0.05 compared to placebo

Figure 1. Percent Change From Baseline in Lumbar Spine (L1-L4) BMD Over 24 Months

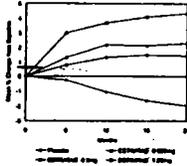
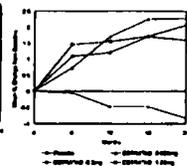


Figure 2. Percent Change From Baseline in Hip BMD Over 24 Months



INFORMATION REGARDING ENDOMETRIAL EFFECTS: As shown in Table 3, only one case of endometrial hyperplasia occurred in the groups treated with placebo or unopposed 0.3 mg ESTRATAB[®] Tablets. The incidence of endometrial hyperplasia was significantly greater with unopposed ESTRATAB[®] Tablets in doses of 0.625 mg and 1.25 mg.

Table 3. Incidence of Endometrial Hyperplasia After 1 and 2 Years

	Incidence of Hyperplasia				
	No. Pat.	1 Year		2 Years	
		N	%	N	%
Placebo	50	1	1.87	1	1.81
ESTRATAB [®] 0.3 mg	59	1	1.69	1	1.69
ESTRATAB [®] 0.625 mg	59	12	20.3**	17	28.8**
ESTRATAB [®] 1.25 mg	60	26	43.3**	32	53.3**

* p<0.05 compared to baseline
* p<0.05 compared to ESTRATAB[®] 0.3 mg

INFORMATION REGARDING LIPID EFFECTS: As shown in Table 4, ESTRATAB[®] Tablets increase HDL cholesterol and decrease LDL cholesterol. The following table summarizes mean percent changes from baseline values after 2 years of treatment.

Table 4. Mean Percent Change From Baseline in Lipid Parameters After Two Years

	Lipid Parameters			
	HDL Cholesterol	LDL Cholesterol	Triglycerides	Total Cholesterol
Placebo	7.64	1.72	17.34*	1.88
ESTRATAB [®] 0.3 mg	5.59*	-4.62**	15.02*	-1.88
ESTRATAB [®] 0.625 mg	10.54**	-3.71	18.02*	0.08
ESTRATAB [®] 1.25 mg	12.31**	-14.71**	28.77*	-5.15**

* p<0.05 compared to baseline
* p<0.05 compared to placebo

INDICATIONS AND USAGE

ESTRATAB[®] Tablets are indicated in the:

- Treatment of moderate to severe vasomotor symptoms associated with the menopause. (There is no adequate evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause, and they should not be used to treat these conditions).
- Treatment of vulval and vaginal atrophy.
- Treatment of hypostrogenism due to hypogonadism, castration, or primary ovarian failure.
- Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.

ADVERSE EFFECTS

- Elevated Blood Pressure:** Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. One study showed that postmenopausal estrogen users have higher blood pressure than non-users. Two other studies showed slightly lower blood pressure among estrogen users compared to non-users. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use.
- Hypersensitization:** Administration of estrogens may lead to severe hypersensitivity in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

PRECAUTIONS

General

1. **Addition of a progestin:** Studies of the addition of a progestin for ten 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. Morphological and biochemical studies of endometria suggest that 10 to 14 days of progestin are needed to provide maximal maturation of the endometrium and to reduce the likelihood of hyperplastic changes.

There are, however, possible risks which may be associated with the use of progestins in estrogen replacement regimens. These include:

- adverse effects on lipoprotein metabolism lowering HDL and raising LDL which could diminish the purported cardiovascular protective effects of estrogen therapy (see PRECAUTIONS below);
- impairment of glucose tolerance; and
- possible enhancement of mitotic activity in breast epithelial tissue, although few epidemiological data are available to address this point (see PRECAUTIONS below).

The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects, but these issues will require further study before they are clarified.

2. **Cardiovascular risk:** A causal relationship between estrogen replacement therapy and reduction of cardiovascular disease in postmenopausal women has not been proven. Furthermore, the effect of added progestins on this putative benefit is not yet known.

In recent years many published studies have suggested that there may be a cause-effect relationship between postmenopausal oral estrogen replacement therapy without added progestins and a decrease in cardiovascular disease in women. Although most of the observational studies which assessed this statistical association have reported a 20% to 50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports:

- Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to estrogen replacement therapy. It may instead have been caused by life-style and medical characteristics of the women studied with the result that healthier women were selected for estrogen therapy. In general, treated women were of higher socioeconomic and educational status, more physically active, more likely to have undergone surgical menopause, and less likely to have diabetes than the untreated women. Although some studies attempted to control for these selection factors, it is common for properly designed randomized trials to fail to confirm benefits suggested by less rigorous study designs. Thus, ongoing and future large-scale randomized trials may fail to confirm this apparent benefit.
- Current medical practice often includes the use of concomitant progestin therapy in women with intact uteri (see PRECAUTIONS and WARNINGS). While the effects of added progestins on the risk of ischemic heart disease are not known, all available progestins reverse at least some of the favorable effects of estrogens on HDL and LDL levels.
- While the effects of added progestins on the risk of breast cancer are also unknown, available epidemiological evidence suggests that progestins do not reduce, and may enhance, the moderately increased breast cancer incidence that has been reported with prolonged estrogen replacement therapy (see WARNINGS above).

Because relatively long-term use of estrogens by a woman with a uterus has been shown to induce endometrial cancer, physicians often recommend that women who are diagnosed candidates for hormone replacement should take progestins as well as estrogens. When considering prescribing concomitant estrogens and progestins for hormone replacement therapy, physicians and patients are advised to carefully weigh the potential benefits and risks of the added progestin. Large-scale randomized, placebo-controlled, prospective clinical trials are required to clarify these issues.

- Physical Examination:** A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pre-treatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without reexamining the patient.
- Hypocoagulability:** Some studies have shown that women taking estrogen replacement therapy have hypocoagulability, primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have increased coagulation parameters at baseline compared to premenopausal women. There is some suggestion that low-dose postmenopausal treatment may increase the risk of thromboembolism, although the majority of studies (of primarily conjugated estrogen users) reports no such increase. There is insufficient information on hypocoagulability in women who have had previous thromboembolic disease.
- Familial hypertriglyceridemia:** Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.

- 6. **Fluid retention:** Because estrogen may cause some degree of fluid retention, conditions which might be exacerbated by this factor such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.
- 7. **Uterine bleeding and metaplasia:** Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding, and metaplasia.
- 8. **Impaired liver function:** Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution.

Information for the Patient
See text of Patient Package Insert below which appears after the NOW SUPPLIED section.

Laboratory Tests

Estrogen administration should generally be guided by clinical response at the smallest dose, rather than laboratory monitoring, for total of symptoms for these indications in which symptoms are observable. For prevention of osteoporosis, however, see **DOSEAGE AND ADMINISTRATION** section.

Breast/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, II-VIII 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 T3 concentrations are unaltered.
- 3. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
- 4. Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.
- 5. Impaired glucose tolerance.
- 6. Reduced response to methylxanthine test.
- 7. Reduced serum folate concentration.

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

Pregnancy Category X
Estrogens should not be used during pregnancy. See **CONTRAINDICATIONS** and **Boned Warning**.

Nursing Mothers

As a general principle, 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.

ADVERSE REACTIONS

The following additional adverse reactions have been reported with estrogen therapy (See **WARNINGS** regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gallbladder disease, cardiovascular disease, elevated blood pressure, and hypercalcemia.)

- 1. **Genitourinary system:**
Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow.
Breakthrough bleeding, spotting.
Increase in size of uterine leiomyomata.
Vaginal candidiasis.
Change in amount of cervical secretion.
- 2. **Breasts:**
Tenderness, enlargement.
- 3. **Gastrointestinal:**
Nausea, vomiting.
Abdominal cramps, bloating.
Cholelithiasis.
Increased incidence of gallbladder disease.
- 4. **Skin:**
Chloasma or melasma which may persist when drug is discontinued.
Erythema multiforme.
Erythema nodosum.
Hemorrhagic eruption.
Loss of scalp hair.
Hirsutism.
- 5. **Eyes:**
Steepening of corneal curvature.
Intolerance to contact lenses.
- 6. **CRS:**
Headache, migraine, dizziness.
Mental depression.
Chorea.
- 7. **Miscellaneous:**
Increase or decrease in weight.
Reduced carbohydrate tolerance.
Aggravation of porphyria.
Edema.
Changes in libido.

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.

DOSEAGE AND ADMINISTRATION

1. **Given orally:** For short term use only:
For treatment of moderate to severe vasomotor symptoms, atrophic vaginitis, or atrophic vulva associated with the menopause. The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible. Administration should be cyclic (e.g., three weeks on and one week off). Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage ranges:

Vasomotor symptoms - 1.25 mg daily, if the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding.

Atrophic vaginitis and atrophic vulva - 0.3 mg to 1.25 mg or more daily, depending upon the tissue response of the individual patient. Administer cyclically.

2. **Given orally:** Female hypogonadism; female castration; primary ovarian failure.

Usual dosage ranges:

Female hypogonadism - 2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with **ESTRATAB®** (Ethinodiol Estrogens Tablets, USP), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

proved for the medicine prescribed for you, ask your doctor or pharmacist to show you the professional labeling.
You can also look up the specific estrogen product in a book called the "Physicians' Desk Reference", which is available in many book stores and public libraries. (Generic drugs carry virtually the same labeling information as their brand name versions).

To reduce moderate or severe menopausal symptoms:

Estrogens are hormones made by the ovaries of normal women. Between ages 45 and 55, the ovaries normally stop making estrogens. This leads to a drop in body estrogen levels which causes the "change of life" or menopause (the end of monthly menstrual periods). If both ovaries are removed during an operation before natural menopause takes place, the sudden drop in estrogen levels causes "surgical menopause".

When the 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"). Using estrogen drugs can help the body adjust to lower estrogen levels and reduce these symptoms. Most women who have only mild menopausal symptoms or none at all do not need to use estrogen drugs for these symptoms. Others may need to take estrogens for a few months while their bodies adjust to lower estrogen levels. The majority of women do not need estrogen replacement for longer than six months for these symptoms.

To treat **vulval and vaginal atrophy** (itching, burning, dryness in or around the vagina, difficulty or burning on urination) associated with menopause.

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

To treat certain types of abnormal vaginal bleeding due to hormonal imbalance when your doctor has found no serious cause of the bleeding.

To treat certain cancers in special situations, in men and women.

To prevent **thinning of bones:** Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. The bones of the spine, wrists and hips break most often from osteoporosis. Both men and women start to lose bone mass after about age 40, but women lose bone mass faster after the menopause. Using estrogens after the menopause slows down bone thinning and may prevent bones from breaking. Lifelong adequate calcium intake, either in the diet (such as dairy products) or by calcium supplements (to reach a total daily intake of 1000 milligrams per day before menopause or 1500 milligrams per day after menopause), may help to prevent osteoporosis. Regular weight-bearing exercise (like walking and running for an hour, two or three times a week) may also help to prevent osteoporosis. Before you change your calcium intake or exercise habits, it is important to discuss these lifestyle changes with your doctor to find out if they are safe for you.

Since estrogen use has some risks, only women who are likely to develop osteoporosis should use estrogens for prevention. Women who are likely to develop osteoporosis often have the following characteristics: white or Asian race, slim, cigarette smoker, and a family history of osteoporosis in a mother, sister, or aunt. Women who have relatively early menopause, often because their ovaries were removed during an operation ("surgical menopause"), are more likely to develop osteoporosis than women whose menopause happens at the average age.

WHO SHOULD NOT USE ESTROGENS

Estrogens should not be used:

During pregnancy (see **Boned Warning**). If you think you may be pregnant, do not use any form of estrogen. Using estrogens while you are pregnant may cause your unborn child to have birth defects. Estrogens do not prevent miscarriage.

If you have **unusual vaginal bleeding** which has not been evaluated by your doctor (see **Boned Warning**). Unusual vaginal bleeding can be a warning sign of cancer of the uterus, especially if it happens after menopause. Your doctor must find out the cause of the bleeding so that he or she can recommend the proper treatment. Taking estrogens without seeing your doctor can cause you serious harm if your vaginal bleeding is caused by cancer of the uterus.

If you have **had cancer.** Since estrogens increase the risk of certain types of cancers, you should not use estrogens if you have ever had cancer of the breast or uterus, unless your doctor recommends that the drug may help in the cancer treatment. For certain patients with breast or prostate cancer, estrogens may help.

If you have **any circulation problems.** Estrogen drugs should not be used except in unusually special situations in which your doctor judges that you need estrogen therapy so much that the risks are acceptable. Men and women with abnormal blood clotting conditions should avoid estrogen use (see **DANGERS OF ESTROGENS**, below).

When they do not work: During menopause, some women develop nervous symptoms or depression. Estrogens do not relieve these symptoms. You may have heard that taking estrogens for years after menopause will keep your skin soft and supple and keep you feeling young. There is no evidence for these claims and such long-term estrogen use may have serious risks.

After **childbirth or when breastfeeding a baby.** Estrogens should not be used to try to stop the breasts from filling with milk after a baby is born. Such treatment may increase the risk of developing blood clots (see **DANGERS OF ESTROGENS**, below).

If you are **breastfeeding**, you should avoid using any drugs because many drugs pass through to the baby in the milk. While nursing a baby, you should take drugs only on the advice of your health care provider.

DANGERS OF ESTROGENS

Cancer of the uterus: Your risk of developing cancer of the uterus gets higher the longer you use estrogens and the larger doses you use. One study showed that after women stop taking estrogens, this higher cancer risk quickly returns to the usual level of risk (as if you had never used estrogen therapy). These other studies showed that the cancer risk stayed high for 8 to more than 15 years after stopping estrogen treatment. Because of this risk, IF YOU STOP, YOU WANT TO TAKE THE LOWEST DOSE THAT WORKS AND TO TAKE IT ONLY AS LONG AS YOU NEED IT.

Using progestin therapy together with estrogen therapy may reduce the higher risk of uterine cancer related to estrogen use (but see **OTHER INFORMATION**, below).

If you have had your uterus removed (total hysterectomy), there is no danger of developing cancer of the uterus.

Cancer of the breast: Most studies have not shown a higher risk of breast cancer in women who have ever used estrogens. However, some studies have reported that breast cancer developed more often (up to twice the usual rate) in women who used estrogens for long periods of time (especially more than 10 years), or who used higher doses for shorter time periods.

Regular breast examinations by a health professional and monthly self-examination are recommended for all women.

Gallbladder disease: Women who use estrogens after menopause are more likely to develop gallbladder disease needing surgery than women who do not use estrogens.

Abnormal blood clotting: Taking estrogens may cause changes in your blood clotting system. These changes allow the blood to clot more easily, possibly allowing clots to form in your bloodstream. If blood clots do form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to the brain), a heart attack (by cutting off blood to the heart), a pulmonary embolus (by cutting off blood to the lungs), or other problems. Any of these conditions may cause death or serious long term disability. However, most studies of low dose estrogen use by women do not show an increased risk of these complications.

SIDE EFFECTS

In addition to the risks listed above, the following side effects have been reported with estrogen use:

- Nausea, vomiting
- Breast tenderness or enlargement
- Enlargement of benign tumors ("fibroids") of the uterus.
- Retention of excess fluid. This may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease, or kidney disease.
- A spotty darkening of the skin, particularly on the face.

REDUCING RISK OF ESTROGEN USE

If you use estrogens for your risks by doing these things:
See your doctor regularly. While you are using estrogens, it is important to visit your doctor at least once a year for a check-up. If you develop vaginal bleeding while taking estrogens, 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

that will control symptoms should be chosen. Discontinue use as soon as possible. Administration should be cyclic (i.e., three weeks on and one week off). Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage ranges:
Vasomotor symptoms - 1.25 mg daily. If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding.

Atrophic vaginitis and breast pain: - 0.3 mg to 1.25 mg or more daily, depending upon the tissue response of the individual patient. Administer cyclically.

2. **Given cyclically:** Female hypogonadism; female castration; primary ovarian failure.

Usual dosage ranges:
Female hypogonadism - 2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with ESTRATAB® (Esterified Estrogens Tablets, USP), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last few days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the 5th day of bleeding.

Female castration, and primary ovarian failure - 1.25 mg daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

3. **Given chronically:** Inoperable progressing prostatic cancer - 1.25 to 2.5 mg three times daily. The effectiveness of therapy can be judged by prostatic determinations as well as by symptomatic improvement of the patient. Inoperable progressing breast cancer in appropriately selected men and postmenopausal women. (See CONTRAINDICATIONS) - Suggested dosage is 10 mg three times daily for a period of at least three months.

4. **For prevention of osteoporosis**—therapy with ESTRATAB® Tablets to prevent postmenopausal bone loss should be initiated as soon as possible after menopause. Therapy should be initiated at a daily dose of 0.3 mg and may be increased to a minimum daily dose of 1.25 mg if necessary to control concurrent menopausal symptoms.

Discontinuation of estrogen replacement therapy may re-establish the natural rate of bone loss.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer, and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

NOW SUPPLIED
ESTRATAB® (Esterified Estrogens Tablets, USP) Tablets are available in the following strengths and package sizes:

- Each blue tablet with black imprint "SOLVAY 1014" contains 0.3 mg, in bottles of 100 (NDC 0032-1014-01).
- Each yellow tablet with black imprint "SOLVAY 1023" contains 0.625 mg, in bottles of 100 (NDC 0032-1023-01) and 1000 (NDC 0032-1023-10).
- Each light purple tablet with white imprint "SOLVAY 1025" contains 2.5 mg, in bottles of 100 (NDC 0032-1025-01).

Storage
Store and dispense in light, light-resistant containers as defined in the USP. Store below 30°C (86°F). Protect from moisture.

R_x only

Manufactured by:

Solvay
Pharmaceuticals, Inc.
Menafite, GA 30082

INFORMATION FOR THE PATIENT

This leaflet describes when and how to use estrogens and the risks of estrogen treatment.

Estrogens have important benefits but also some risks. You must decide, with your doctor, whether the risks to you of estrogen use are acceptable because of their benefits. If you use estrogens, check with your doctor to make sure you are using the lowest possible dose that works, and that you don't use them for longer than necessary. How long you need to use estrogens will depend on the reason for use.

1. ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS IN WOMEN WHO HAVE HAD THEIR MENOPAUSE ("CHANGE OF LIFE")

If you use any estrogen-containing drug, it is important to visit your doctor regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your doctor should evaluate any unusual vaginal bleeding to find out the cause.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

Estrogens do not prevent miscarriage (spontaneous abortion) and are not needed in the days following childbirth. If you take estrogens during pregnancy, your unborn child has a greater than usual chance of having birth defects. The risk of developing these defects is small, but clearly larger than the risk in children whose mothers did not take estrogen during pregnancy. These birth defects may affect the baby's urinary system and sex organs. Daughters born to mothers who took DES (an estrogen drug) have a higher than usual chance of developing cancer of the vagina or cervix when they become teenagers or young adults. Sons may have a higher than usual chance of developing cancer of the testicles when they become teenagers or young adults.

USES OF ESTROGEN
NOT EVERY ESTROGEN DRUG IS APPROVED FOR EVERY USE LISTED IN THIS SECTION. If you want to know which of these possible uses are ap-

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prohibited, ask your doctor. Women who use estrogen should not use estrogen if they have had gallbladder disease needing surgery than women who do not use estrogen.

Abnormal blood clotting. Taking estrogens may cause changes in your blood clotting system. These changes allow the blood to clot more easily, possibly allowing clots to form in your bloodstream. If blood clots do form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to the brain), a heart attack (by cutting off blood to the heart), a pulmonary embolus (by cutting off blood to the lungs), or other problems. Any of these conditions may cause death or serious long term disability. However, most studies of low dose estrogen usage by women do not show an increased risk of these complications.

SIDE EFFECTS

In addition to the risks listed above, the following side effects have been reported with estrogen use:

- Nausea, vomiting
- Breast tenderness or enlargement
- Enlargement of benign tumors ("fibroids") of the uterus
- Retention of excess fluid. This may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease, or kidney disease.
- A spotty darkening of the skin, particularly on the face.

REDUCING RISK OF ESTROGEN USE

If you use estrogens, you can reduce your risks by doing these things:
• If you use estrogens, you can reduce your risks by doing these things:
• See your doctor regularly. While you are using estrogens, it is important to visit your doctor at least once a year for a check-up. If you develop vaginal bleeding while taking estrogens, 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.

Reassess your need for estrogens. You and your doctor should reevaluate whether or not you still need estrogens at least every six months.

Be alert for signs of trouble. If any of these warning signals for any other unusual symptoms happen while you are using estrogens, call your doctor immediately:

- Abnormal bleeding from the vagina (possible uterine cancer)
- Pains in the calves or chest, sudden shortness of breath, or coughing blood (possible clot in the legs, heart, or lungs)
- Severe headache or vomiting, dizziness, faintness, changes in vision or speech, weakness or numbness of an arm or leg (possible clots in the brain or eyes)
- Breast lumps (possible breast cancer; ask your doctor or health professional to show you how to examine your breasts monthly)
- Yellowing of the skin or eyes (possible liver problem)
- Pain, swelling, or tenderness in the abdomen (possible gallbladder problem)

OTHER INFORMATION

Estrogens increase the risk of developing a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus. Taking progestins, another hormone drug, with estrogens lowers the risk of developing the condition. Therefore, if your uterus has not been removed, your doctor may prescribe a progestin for you to take together with the estrogen.

You should know, however, that taking estrogens with progestins may have additional risks. These include:

- Unhealthy effects on blood fats (especially the lowering of HDL blood cholesterol, the "good" blood fat which protects against heart disease)
- Unhealthy effects on blood sugar (which might make a diabetic condition worse); and
- A possible further increase in breast cancer risk which may be associated with long-term estrogen use.

Some research has shown that estrogens taken without progestins may protect women against developing heart disease. However, this is not certain. The protection shown may have been caused by the characteristics of the estrogen-treated women, and not by the estrogen treatment itself. In general, treated women were slimmer, more physically active, and were less likely to have diabetes than the untreated women. These characteristics are known to protect against heart disease.

You are cautioned to discuss very carefully with your doctor or health care provider all the possible risks and benefits of long-term estrogen and progestin treatment as they affect you personally.

Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.

If you will be taking calcium supplements as part of the treatment to help prevent osteoporosis, check with your doctor about how much to take.

Keep this and all drugs out of the reach of children. In case of overdose, call your doctor, hospital, or poison control center immediately.

This leaflet provides a summary of the most important information about estrogens. If you want more information, ask your doctor or pharmacist to show you the professional labeling. The professional labeling is also published in a book called the "Physician's Desk Reference," which is available in book stores and public libraries. Generic drugs carry virtually the same labeling information as their brand name versions.

NOW SUPPLIED
ESTRATAB® (Esterified Estrogens Tablets, USP) for oral administration.
Each blue tablet contains 0.3 mg.
Each yellow tablet contains 0.625 mg.
Each light purple tablet contains 2.5 mg.

R_x only

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7E Rev 2/98

Solvay
Pharmaceuticals, Inc.
Menafite, GA 30082

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PATIENT INFORMATION WHAT YOU SHOULD KNOW ABOUT ESTROGENS ESTRATAB® (Esterified Estrogens)

INFORMATION FOR THE PATIENT

This leaflet describes when and how to use estrogens and the risks of estrogen treatment.

Estrogens have important benefits but also some risks. You must decide, with your doctor, whether the risks to you of estrogen use are acceptable because of their benefits. If you use estrogens, check with your doctor to make sure you are using the lowest possible dose that works, and that you don't use them for longer than necessary. How long you need to use estrogens will depend on the reason for use.

1. ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS IN WOMEN WHO HAVE HAD THEIR MENOPAUSE ("CHANGE OF LIFE")

If you use any estrogen-containing drug, it is important to visit your doctor regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your doctor should evaluate any unusual vaginal bleeding to find out the cause.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

Estrogens do not prevent miscarriage (spontaneous abortion) and are not needed in the days following childbirth. If you take estrogens during pregnancy, your unborn child has a greater than usual chance of having birth defects. The risk of developing these defects is small, but clearly larger than the risk in children whose mothers did not take estrogen during pregnancy. These birth defects may affect the baby's urinary system and sex organs. Daughters born to mothers who took DES (an estrogen drug) have a higher than usual chance of developing cancer of the vagina or cervix when they become teenagers or young adults. Sons may have a higher than usual chance of developing cancer of the testicles when they become teenagers or young adults.

USES OF ESTROGEN

NOT EVERY ESTROGEN DRUG IS APPROVED FOR EVERY USE LISTED IN THIS SECTION. If you want to know which of these possible uses are approved for the medicine prescribed for you, ask your doctor or pharmacist to show you the professional labeling.

You can also look up the specific estrogen product in a book called the "Physicians' Desk Reference", which is available in many book stores and public libraries. (Generic drugs carry virtually the same labeling information as their brand name versions).

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

When the 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". 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 to use estrogen drugs for these symptoms. Others may need to take estrogens for a few months while their bodies adjust to lower estrogen levels. The majority of women do not need estrogen replacement for longer than six months for these symptoms.

To treat vulval and vaginal atrophy (itching, burning, dryness in or around the vagina, difficulty or burning on urination) associated with menopause.

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

To treat certain types of abnormal vaginal bleeding due to hormonal imbalance when your doctor has found no serious cause of the bleeding.

To treat certain cancers in special situations, in men and women.

To prevent thinning of bones. Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. The bones of the spine, wrists and hips break most often in osteoporosis. Both men and women start to lose bone mass after about age 40, but women lose bone mass faster after the menopause. Using estrogens after the menopause slows down bone thinning and may prevent bones from breaking. (Lifestyle adequate calcium intake, either in the diet (such as dairy products) or by calcium supplements to reach a total daily intake of 1000 milligrams per day before menopause or 1500 milligrams per day after menopause), may help to prevent osteoporosis. Regular weight-bearing exercise (like walking and running for an hour, two or three times a week) may also help to prevent osteoporosis. Before you change your calcium intake or exercise habits, it is important to discuss these lifestyle changes with your doctor to find out if they are safe for you.

Since estrogen use has some risks, only women who are likely to develop osteoporosis should use estrogens for prevention. Women who are likely to develop osteoporosis often have the following characteristics: white or Asian race, slim, cigarette smokers, and a family history of osteoporosis in a mother, brother, or aunt. Women who have relatively early menopause, often because their ovaries were removed during an operation ("surgical menopause"), are more likely to develop osteoporosis than women whose menopause happens at the average age.

WHO SHOULD NOT USE ESTROGENS

Estrogens should not be used:

During pregnancy (see Boxed Warning). If you think you may be pregnant, do not use any form of estrogen-containing drug. Using estrogens while you are pregnant may cause your unborn child to have birth defects. Estrogens do not prevent miscarriage.

If you have unusual vaginal bleeding which has not been evaluated by your doctor (see Boxed Warning). Unusual vaginal bleeding can be a warning sign of cancer of the uterus, especially if it happens after menopause. Your doctor must find out the cause of the bleeding so that he or she can recommend the proper treatment. Taking estrogens without visiting your doctor can cause you serious harm if your vaginal bleeding is caused by cancer of the uterus.

If you have had cancer. Since estrogens increase the risk of certain types of cancers, you should not use estrogens if you have ever had cancer of the breast or uterus, unless your doctor recommends that the drug may help in the cancer treatment. (For certain patients with breast or prostate cancer, estrogens may help.)

If you have any circulation problems. Estrogen drugs should not be used except in unusually special situations in which your doctor judges that you need estrogen therapy so much that the risks are acceptable. Men and women with abnormal blood clotting conditions should avoid estrogen use (see DANGERS OF ESTROGENS, below).

When they do not work. During menopause, some women develop nervous symptoms or depression. Estrogens do not relieve these symptoms. You may have heard that taking estrogens for years after menopause will keep your skin soft and supple and keep you feeling young. There is no evidence for these claims and such long-term estrogen use may have serious risks.

After childbirth or when breastfeeding a baby. Estrogens should not be used to try to stop the breasts from leaking with milk after a baby is born. Such treatment may increase the risk of developing blood clots (see DANGERS OF ESTROGENS, below).

If you are breastfeeding, you should avoid using any drugs because many drugs pass through to the baby in the milk. While nursing a baby, you should take drugs only on the advice of your health care provider.

DANGERS OF ESTROGENS

Cancer of the uterus. Your risk of developing cancer of the uterus gets higher the longer you use estrogens and the larger doses you use. One study showed that after women stop taking estrogens, this higher cancer risk quickly returns to the usual level of risk (as if you had never used estrogen therapy). Three other studies showed that the cancer risk stayed high for 8 to more than 15 years after stopping estrogen treatment. Because of this risk, **IT IS IMPORTANT TO TAKE THE LOWEST DOSE THAT WORKS AND TO TAKE IT ONLY AS LONG AS YOU NEED IT.**

Using progestin therapy together with estrogen therapy may reduce the higher risk of uterine cancer related to estrogen use (but see **OTHER INFORMATION**, below).

If you have had your uterus removed (total hysterectomy), there is no danger of developing cancer of the uterus.

Cancer of the breast. Most studies have not shown a higher risk of breast cancer in women who have ever used estrogens. However, some studies have reported that breast cancer developed more often (up to twice the usual rate) in women who used estrogens for long periods of time (especially more than 10 years), or who used higher doses for shorter time periods.

Regular breast examinations by a health professional and monthly self-examination are recommended for all women.

Gallbladder disease. Women who use estrogens after menopause are more likely to develop gallbladder disease needing surgery than women who do not use estrogens.

Abnormal blood clotting. Taking estrogens may cause changes in your blood clotting system. These changes allow the blood to clot more easily, possibly allowing clots to form in your bloodstream. If blood clots do form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to the brain), a heart attack (by cutting off blood to the heart), a pulmonary embolus (by cutting off blood to the lungs), or other problems. Any of these conditions may cause death or serious long term disability. However, most studies of low dose estrogen usage by women do not show an increased risk of these complications.

SIDE EFFECTS

In addition to the risks listed above, the following side effects have been reported with estrogen use:

- Nausea, vomiting.
- Breast tenderness or enlargement.
- Enlargement of benign tumors ("fibroids") of the uterus.
- Retention of excess fluid. This may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease, or kidney disease.
- A spotty darkening of the skin, particularly on the face.

REDUCING RISK OF ESTROGEN USE

If you use estrogens, you can reduce your risks by doing these things:
See your doctor regularly. While you are using estrogens, it is important to visit your doctor at least once a year for a check-up. If you develop vaginal bleeding while taking estrogens, 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.

Reassess your need for estrogens. You and your doctor should re-evaluate whether or not you still need estrogens at least every six months.

Be alert for signs of trouble. If any of these warning signals for any other unusual symptoms happen while you are using estrogens, call your doctor immediately:

- Abnormal bleeding from the vagina (possible uterine cancer).
- Pains in the calves or chest, sudden shortness of breath, or coughing blood (possible clot in the legs, heart, or lungs).
- Severe headache or vomiting, dizziness, lightheadedness, changes in vision or speech, weakness or numbness of an arm or leg (possible clots in the brain or eye).
- Breast lumps (possible breast cancer; ask your doctor or health professional to show you how to examine your breasts monthly).
- Yellowing of the skin or eyes (possible liver problem).
- Pain, swelling, or tenderness in the abdomen (possible gallbladder problem).

OTHER INFORMATION

Estrogens increase the risk of developing a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus. Taking progestins, another hormone drug, with estrogens lowers the risk of developing this condition. Therefore, if your uterus has not been removed, your doctor may prescribe a progestin for you to take together with the estrogen.

You should know, however, that taking estrogens with progestins may have additional risks. These include:

- unhealthy effects on blood fats (especially the lowering of HDL blood cholesterol, the "good" blood fat which protects against heart disease),
- unhealthy effects on blood sugar (which might make a diabetic condition worse); and
- a possible further increase in breast cancer risk which may be associated with long-term estrogen use.

Some research had shown that estrogens taken without progestins may protect women against developing heart disease. However, this is not certain. The protection shown may have been caused by the characteristics of the estrogen-treated women, and not by the estrogen treatment itself. In general, treated women were slimmer, more physically active, and were less likely to have diabetes than the untreated women. These characteristics are known to protect against heart disease.

You are cautioned to discuss very carefully with your doctor or health care provider all the possible risks and benefits of long-term estrogen and progestin treatment as they affect you personally.

Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.

If you will be taking calcium supplements as part of the treatment to help prevent osteoporosis, check with your doctor about how much to take.

Keep this and all drugs out of the reach of children. In case of overdose, call your doctor, hospital, or poison control center immediately.

This leaflet provides a summary of the most important information about estrogens. If you want more information, ask your doctor or pharmacist to show you the professional labeling. The professional labeling is also published in a book called the "Physicians' Desk Reference," which is available in book stores and public libraries. Generic drugs carry virtually the same labeling information as their brand name versions.

HOW SUPPLIED

ESTRATAB® (Esterilized Estrogens Tablets, USP) for oral administration.

Each blue tablet contains 0.3 mg.

Each yellow tablet contains 0.625 mg.

Each light purple tablet contains 2.5 mg.

R_x only

The appearance of ESTRATAB® Tablets is a trademark of Solvay Pharmaceuticals, Inc.

7E Rev 2/86

Solvay
Pharmaceuticals, Inc.
Manhasset, MA 01946

©1986 Solvay Pharmaceuticals, Inc.

May 5, 1997

Jennifer Wegener Phillips, Pharm.D.
Director, Regulatory Affairs
Solvay Pharmaceuticals, Inc.
901 Sawyer Road
Marietta, GA 30062

Dear Dr. Phillips:

Re: ESTRATAB® (Esterified Estrogens Tablets, USP)
ANDA 86-715/S-030 (0.3 mg)
ANDA 83-209/S-054 (0.625 mg)

Amendment to Supplemental Applications:
Environmental Assessment

Review of your environmental assessment, which was submitted on February 10, 1997, has been completed. The following additional information is requested.

1. Please provide additional details in item 4.c for the four production locations, to include environments, zoning, and geographic features.
2. Section 5.b and Appendix 2 do not agree regarding the CAS number for estrone sodium sulfate.
3. Please specify the particular _____ used, in Appendix 2.
4. CAS numbers should be provided for the impurities listed in Appendix 3.
5. Potential residual solvents should be identified in Section 5.h, or Section 6.a, or an appendix.
6. Item 6.b should provide additional details regarding controls on emissions that could be released via the air and liquid waste streams.
7. Item 6.c should include a list of all applicable Federal, State, and local emission requirements for the four production locations. Item 6.c should also include a list of emission permits and/or licenses (with numbers, expiration dates and authorizing agencies) for the on-site facilities.
8. Discussion of the effect of approval of these supplemental applications, in item 6.d, should include an estimate of the subsequent increase in production at the four facilities, relative to current production.

9. The certification in item 13 should acknowledge that non-confidential information will be made available to the public.

Designate your response as an amendment to these supplemental applications.

If you respond before May 16, 1997, please direct your response to Mr. Mark Anderson, supervisory project manager, OGD. A later response should be directed to Mr. Joseph Buccine, project manager, OGD.

X:\NEW\FIRMSNZ\SOLVAY\LTRS&REV\86715S30.IR1



SOLVAY

SOLVAY PHARMACEUTICALS

February 10, 1997

Mr. Douglas L. Sporn, Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

NDA SUPPL AMENDMENT

**SOLVAY
EA**

Dear Mr. Sporn:

RE: **ESTRATAB® (Esterified Estrogens Tablets, USP)**
ANDA 86-715/S-030 (0.3 mg),
ANDA 83-209/S-054 (0.625 mg)

Amendment to Supplemental Application: Environmental Assessment

Reference is made to the above Abbreviated New Drug Applications for **ESTRATAB® (Esterified Estrogens Tablets, USP)**. Further reference is made to the telephone conversations on January 28 and February 3, 1997, between Ms. Nancy Sager of your office and Alvin Howard, Joey Pollock, and Don Ruggirello of Solvay Pharmaceuticals, Inc.

As requested by Ms. Sager, Solvay Pharmaceuticals, Inc., is submitting an environmental assessment as an amendment to our pending supplemental applications. This assessment has been prepared in accordance with the guidance provided by Ms. Sager.

This information is being submitted only to the **ESTRATAB® 0.3 mg** product, ANDA 86-715/S-030. By way of this cover letter, we are cross-referencing the following applications: **ESTRATAB® 0.625 mg**, ANDA 83-209/S-054.

Should you have any questions, please contact Mr. Alvin Howard at (770) 578-5661.

Sincerely,

Jennifer Wegener Phillips
Jennifer Wegener Phillips, Pharm.D.
Director, Regulatory Affairs

EBS38155.041

RECEIVED
FEB 12 1997
GENERIC DRUGS

July 31, 1997

VIA HAND DELIVERY

NDA SUPPL AMENDMENT FPL

Mr. Jerry Phillips, Director
Division of Labeling and Program Support
Office of Generic Drugs, CDER
Food and Drug Administration
Metro Park North 2
7500 Standish Place
Rockville, MD 20855

FPL
9/1/97

Dear Mr. Phillips:

RE: **ESTRATAB® (Esterified Estrogens Tablets, USP)**
ANDA 86-715/S-030 (0.3 mg)
ANDA 83-209/S-054 (0.625 mg)

MINOR AMENDMENT: Final Printed Labeling

Reference is made to the above-referenced supplemental applications for the Abbreviated New Drug Applications for ESTRATAB® (Esterified Estrogens Tablets, USP) which provide for the indication of prevention of osteoporosis in postmenopausal women. Reference also is made to a July 30, 1997, telephone conversation between Adolph Vezza of your Division and Anisa Dhalla of Solvay Pharmaceuticals, Inc. During this conversation, Mr. Vezza requested final printed labeling for the pending supplements and stated that an approval letter would be issued after receipt of acceptable labeling.

In addition, reference is made to a July 29, 1997, telephone conversation between Mr. Vezza and Ms. Dhalla regarding a January 26, 1995, labeling supplement. This supplement provided revisions to the ESTRATAB® label to comply with the 1992 Labeling Guidance for Estrogen Drug Products and was approved on June 18, 1997. Unfortunately, the ESTRATAB® labeling in the osteoporosis supplement did not contain these revisions. Mr. Vezza recommended that these changes, as well as those from the osteoporosis supplements, be incorporated in the attached final printed labeling for ESTRATAB® Tablets.

ESTRATAB® Tablets
July 31, 1997
Page 2 of 2

Enclosed are the following items:

- Attachment I: Twelve (12) copies of final printed labeling for physicians' labeling.
- Attachment II: Patient Information.
- Attachment III: Summary of revisions made to labeling since March 29, 1997, with reasons for each change noted.
- Attachment IV: FDA letter dated June 18, 1997, approving revised package insert labeling for ESTRATAB® reflecting changes to be in accord with 1992 Labeling Guidance.
A copy of labeling (6E0977 Rev 12/96) is included.

Should you need additional information, please contact Anisa Dhalla, Manager, Labeling and Submissions, at (770) 578-5931.

Sincerely,



Jennifer Wegener Phillips, Pharm. D.
Director, Regulatory Affairs

JWP/jsw



SOLVAY PHARMACEUTICALS

May 6, 1997

Mr. Douglas L. Sporn, Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

NEW CORRESP

NC to S-054

Dear Mr. Sporn:

RE: **ESTRATAB® (Esterified Estrogens Tablets, USP)**
ANDA 86-715/S-030 (0.3 mg)
~~**ANDA 83-209/S-054 (0.625 mg)**~~

Response to FDA Request

Reference is made to the above Abbreviated New Drug Applications for ESTRATAB® (Esterified Estrogens Tablets, USP) and the amendment to supplemental applications for the environmental assessment submitted February 10, 1997. Reference also is made to telephone conversations held on May 5 and May 6, 1997, with Mark Anderson and Gene Schaefer of your office and Alvin Howard, Joey Pollock and me of Solvay Pharmaceuticals, Inc. Further reference is made to FDA's facsimile dated May 5, 1997. Provided herein is our response to that correspondence, including a revised environmental assessment located in Attachment I.

This information is being submitted only to the ESTRATAB® 0.3 mg product, ANDA 86-715/S-030. By way of this cover letter, we are cross-referencing the following applications: ESTRATAB® 0.625 mg, ANDA 83-209/S-054;

Should you have any questions, please contact Mr. Alvin Howard at (770) 578-5661.

Sincerely,

Jennifer Wegener Phillips, Pharm.D.
Director, Regulatory Affairs

Airborne Express Airbill #5063835965

EBS03205.126

RECEIVED
MAY 07 1997
GENERIC DRUGS

ANDA 86-715/S-030 (0.3 mg)
83-209/S-054 (0.625 mg)

Solvay Pharmaceuticals, Inc.
Attention: J. Greg Perkins
901 Sawyer Road
Marietta, GA 30062

MAY 15 1996



Dear Sir:

This is in reference to your supplemental new drug applications dated March 29, 1996, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug applications for ESTRATAB® (Esterified Estrogens Tablets, USP).

The supplemental applications provide for revised package insert labeling reflecting the addition of the indication of prevention of osteoporosis in postmenopausal women.

We have reviewed these supplemental applications and have the following comments:

We have forwarded your proposed labeling revisions to the Division of Metabolism and Endocrine Drug Products (HFD-510) for their review and comment. When we receive a response for the revised labeling we will notify you. Until that time, no further action will be taken on these supplements.

The material submitted is being retained in our files.

Sincerely yours,

John J. Gorsuch for 5-14-96

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research



SOLVAY
 PHARMACEUTICALS

BIOAVAILABILITY

NDA NO. _____ REF. NO. 22-154

NDA SUPPL FOR Labeling

March 29, 1996

Douglas L. Sporn, Director
 Office of Generic Drugs, HFD-600
 Center for Drug Evaluation and Research
 Food and Drug Administration
 Metro Park North II, Room 150
 7500 Standish Place
 Rockville, MD 20855

RECEIVED

APR 01 1996

Dear Mr. Sporn:

RE: **ESTRATAB® (Esterified Estrogens Tablets, USP)**
ANDA 86-715 (0.3 mg)
ANDA 83-209 (0.625 mg)

Supplemental Application

Reference is made to a March 10, 1995, meeting between representatives of your Division, the Division of Metabolism and Endocrine Drug Products, and Solvay Pharmaceuticals, Inc. As discussed at this meeting, attached is a supplemental application for ESTRATAB® to provide for the indication of prevention of osteoporosis in post-menopausal women.

This application is a multiple supplement, but the submission is being made only to the ESTRATAB® 0.3 mg product, ANDA 86-715. By way of this cover letter, we are cross-referencing the following applications: ESTRATAB® 0.625 mg, ANDA 83-209;

We hereby request a waiver for submission of a copy of the full text supplement to each application.

This supplemental application consists of the following sections:

- Section 1 Index.
- Section 2 Labeling.
- Section 8 Clinical Data.
- Section 10 Statistical Section. Section 8 and Section 10 are identical in content. Reference is made to a February 12, 1996, telephone conversation between Dr. Jack Roger, Solvay Pharmaceuticals, Inc., and Dr. Jason Gross of your Division during which the following agreement was reached: Solvay Pharmaceuticals, Inc., should submit Section 8 in its entirety and properly reference Section 8 to Section 10 since both sections are identical in content.
- Section 11 Case Report Tabulations and Patient Profiles.
- Section 12 Case Report Forms and Patient Narratives. Sections 11 and 12 are submitted by electronic version only. Reference is made to a January 31, 1996, letter to FDA requesting waiver of the requirement to submit paper copies of Sections 11 and 12 (Attachment I).
- Section 14 Patent Certification [21 U.S.C. 355 (b) (2) or (j) (2) (A)] and request for three years of exclusivity.

A computer-assisted version of this application ("CANDA") also will be provided. The information provided in this CANDA will be identical to the corresponding information in the hard copy submission. The CANDA will consist of two components, the electronic document and a data review system. Both components have been validated for use in this application. User's guides for these components will be provided during the installation on the Medical Reviewer's computer, which is scheduled for the week of April 8, 1996.

Attachment II contains a copy of the March 22, 1996, letter to the Division of Information Systems Design describing the CANDA and other information as required by the CANDA Guidance Manual.

ESTRATAB® Tablets
Page 3 of 3
March 29, 1996

This letter also certifies that Solvay Pharmaceuticals, Inc., did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) of Section 306 of the Food, Drug, and Cosmetic Act in connection with this supplemental application for ESTRATAB® Tablets. [Section 306(k)(1) of the Generic Drug Enforcement Act (21 U.S.C. 335a(k)(1))].

Should you have questions or need additional clarification, please contact L. Jack Roger, Ph.D., Sr. Regulatory Scientist, at (770) 578-5934. For questions relating directly to use of the CANDAs, reviewers should contact Joe Nolan, Ph.D., Associate Director, Endocrine Operations, at (770) 578-5614 (office). If Dr. Nolan is not in his office, the caller will have the option of being connected to a pager and leaving a phone number.

Sincerely,



J. Greg Perkins, Ph.D., Vice President
Regulatory Affairs and Quality Assurance

JGP/jsw

PHARMACEUTICALS

March 21, 1997

Mr. Douglas L. Sporn, Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

NEW CONTROL

Dear Mr. Sporn:

RE: **ESTRATAB[®] (Esterified Estrogens Tablets, USP)**
ANDA 86-715/S-030 (0.3 mg)
ANDA ~~83~~-209/S-054 (0.625 mg)

**Amendment to Supplemental Application: Prevention of Osteoporosis
Response to FDA Request: *In Vivo* Bioavailability**

Reference is made to our Supplemental Application submitted March 29, 1996, for ESTRATAB[®] (Esterified Estrogens Tablets, USP) for the indication of prevention of osteoporosis. Reference also is made to the telephone conversation on March 18, 1997, between Ms. Cecelia Parise of your Division and Dr. Jack Roger of Solvay Pharmaceuticals, Inc. During this conversation Ms. Parise requested that, in accordance with 21 CFR §320.21, we submit evidence of *in vivo* bioavailability or request a waiver for such a submission.

Reference also is made to the telephone conversation regarding *in vivo* bioavailability data on March 19, 1997, between Mr. Donald Hare of your Division and Drs. Greg Perkins and Jennifer Phillips of Solvay Pharmaceuticals, Inc. Mr. Hare requested that we fulfill §21 CFR 320.21 by submitting evidence of *in vivo* bioavailability. As discussed with Mr. Hare, our January 16, 1997, submission contained report CR100.00.53 entitled "Plasma Concentrations of Estradiol, Total Estrone, and Total Equilin in a Subset of Patients Enrolled in a Two-Year Double-Blind, Placebo Controlled Investigation of the Efficacy and Safety of Three Doses of Esterified Estrogens (ESTRATAB[®]) on Bone Density and Parameters of Bone Metabolism in Postmenopausal Women." This pharmacokinetic report presents plasma concentrations of estrogens measured in a subset of the patients studied in our osteoporosis study (RR.008.00.02). This study provides the evidence of *in vivo* bioavailability for ESTRATAB[®] in the prevention of osteoporosis and fulfills §21 CFR 320.21. Therefore, in response to this request, we refer the Agency to our January 16, 1997, submission.

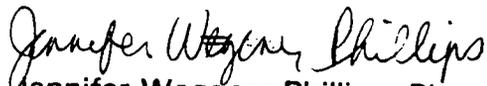
EBS38085.080

ANDA 86-715/S-030
March 21, 1997
Page 2 of 2

This information is being submitted only to the ESTRATAB® 0.3 mg product, ANDA 86-715. By way of this cover letter, we are cross-referencing the following applications: ESTRATAB® 0.625 mg, ANDA 83-209.

Should you have any questions, please contact Jack Roger, Ph.D., Senior Regulatory Scientist, at (770) 578-5934.

Sincerely,


Jennifer Wegener Phillips, Pharm.D.
Director, Regulatory Affairs

JWP/jsw

Airborne Express Airbill #5063832465



**SOLVAY
PHARMACEUTICALS**

December 20, 1996

Mr. Douglas L. Sporn, Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

Dear Mr. Sporn:

NEW CORRESP

RE: **ESTRATAB® (Esterified Estrogens Tablets, USP)**
ANDA 86-715/S-030 (0.3 mg)
ANDA 83-209/S-054 (0.625 mg)

**Amendment to Supplemental Application: Prevention of Osteoporosis
Response to FDA Request**

Reference is made to our supplemental application submitted March 29, 1996, for ESTRATAB® (Esterified Estrogens Tablets, USP) for the indication of prevention of osteoporosis. Reference also is made to our November 21, 1996, amendment that described the amounts of sodium estrone sulfate and sodium equilin sulfate in the ESTRATAB® tablets used in the osteoporosis study (RR.008.00.02). Further reference is made to Mr. Mike Smela's request for Certificates of Analysis (COA's) for the ESTRATAB® study medication to include the following components: 17α -estradiol, 17α -dihydroequilin, 17α -dihydroequilenin, and equilenin.

Please note that the method used in these analyses was qualified to establish linearity, precision, and accuracy for the measurement of these four components over the ranges reported.

Attachment I contains copies of the COA's for the following:

- four expired lots used in the osteoporosis study:

ESTRATAB® 0.3 mg - lots 83921 and 84650
ESTRATAB® 0.625 mg - lots 83922 and 84559;

- two recently manufactured lots:

ESTRATAB® 0.3 mg - lot 87720
ESTRATAB® 0.625 mg - lot 87723.

RECEIVED

DEC 23 1996

GENERIC DRUGS

ANDA 86-715/S-030
December 20, 1996
Page 2 of 2

As you requested, this amendment is being submitted only to the ESTRATAB® 0.3 mg product, ANDA 86-715/S-030. By way of this cover letter, we are cross-referencing the following applications: ESTRATAB® 0.625 mg, ANDA 83-209/S-054;

Should you have any questions, please contact Jack Roger, Ph.D., Senior Regulatory Scientist, at (770) 578-5934.

Sincerely,


Jennifer Wegener Phillips, Pharm.D.
Director, Regulatory Affairs