

WHAT'S IT ALL ABOUT?

AN EXPLANATION OF HORMONE THERAPY LAWSUITS

INTRODUCTION

This is the tragic story of Wyeth's deceptive marketing of Hormone Replacement Therapy ("HRT") products and the damage it has done to thousands of women across the country. This narrative is intended to give you a flavor for some of the important issues in the HRT litigation. It is by no means comprehensive. If you are unsure about the meaning of anything you read, *do not hesitate to ask*. There is no such thing as a stupid question and we are more than happy to answer your inquiries.

It is important to note that, while this paper focuses on Wyeth's conduct, other drug manufacturers may be equally liable for injuries caused by HRT. For instance, many women were prescribed a drug called Provera that was often taken in combination with Wyeth's Premarin. Provera, which was manufactured by Pfizer, contributed to the injuries of thousands of women.

This paper is divided into 2 main sections: The first covers a basic understanding of hormones and menopause to give you a perspective of why hormone therapy and this litigation came into being. The second section provides the Wyeth liability story as we know it so far. Again, it is general in nature and the story continues to develop.

THE BASICS OF HORMONES AND MENOPAUSE

How does the female reproductive hormone cycle work?

Beginning at puberty, a woman's ovaries produce natural hormones estrogen and progesterone. The hypothalamus and pituitary glands send messages to the follicle (eggs encased in their sacs) to produce hormones. It works like this: The hypothalamus tracks the level of estrogen and progesterone in the bloodstream. The hypothalamus releases GnRH, which instructs the pituitary gland to generate follicle stimulating hormone (FSH). In turn, the follicle begins producing estrogen. When estrogen rises to a certain level, the hypothalamus gets the message and instructs the pituitary gland to "turn off" follicle stimulating hormone (FSH) and to produce a surge of LH (luteinizing hormone). When LH reaches its peak, a woman ovulates (the body releases an egg from the follicle). Then the follicle begins to produce progesterone in addition to estrogen for a short time. The estrogen/progesterone combination builds up the lining of the uterus. After that, the follicle reduces production of both hormones. As hormone levels in the body decline, the body sloughs off the uterine lining, which marks a woman's period. When the level of hormones drops low enough, the hypothalamus instructs the pituitary gland to stimulate FSH, which starts the process all over again.

The production of hormones slows over time. By age 35, a woman's hormone production has dropped considerably. Progesterone, often called the "feel good" hormone, is the first hormone to decline and drops 120 times more rapidly than estrogen.

Menopause is a life phase through which all women pass. It is the body's process of phasing out the reproductive cycle by reducing natural estrogen. In the average woman's reproductive life, the menopause occurs when she is relatively young, usually between 46 and 62. Because her average life expectancy is 80 years, the consequences of menopause are felt for years after it begins. During menopause, a woman's estrogen level drops sharply. Hot flashes are a common condition of menopause. For some women, hot flashes are just a vague feeling of warmth. For others, the skin suddenly flushes and beads with sweat, while the pulse races. When estrogen levels decline, so does calcium in the skeleton. As a result, the risk of osteoporosis and spine, hip and other fractures goes up. Menopause is a major issue in women's lives.

What is "Hormone Therapy"?

Hormone "Replacement" Therapy or "HRT" is an umbrella term that is used to refer to either the use of the combination of conjugated estrogens (estrogen) and progesterone (progestin), *or* the use of estrogen by itself. This is important, because Wyeth has attempted to confuse these therapies in the media in an attempt to downplay the risks of combination therapy. Estrogen used alone is sometimes referred to in the following ways:

- * Estrogen "replacement" therapy
- * ET
- * Estrogen alone
- * Estrogen unopposed

A major focus of this litigation is the combination use of estrogen and progestin. The combination's use became popular in the 1980s. Progestin is synthetic progesterone. Its chemical name is MedroxyProgesterone Acetate or MPA, The drug Prempro contains both Premarin (estrogen derived from the urine of pregnant mares) and MPA. Before Prempro was marketed, women were given Premarin and MPA in separate doses at the same time. This therapy was commonly called "P and P" for Premarine and Provera or progesterone. Pfizer was the manufacturer of MPA until its patent expired. Here is a breakdown of the forms of progestin that women took in combination with Premarin.

<u>Name of Drug</u>	<u>Type of Drug</u>	<u>Manufacturer</u>
Premarin	Estrogen	Wyeth
Provera	Progestin	Pfizer
Cycrin	Progestin	Wyeth
Prempro	Estrogen + Progestin	Wyeth (Introduced in 1996)
Premphase	Estrogen + Progestin	Wyeth
Generic MPA	Progestin	Barr Laboratories
Generic MPA	Progestin	Greenstone Ltd (sub of Pfizer)

Women who are treated with Hormone Therapy

Women who underwent surgical menopause (i.e., had a hysterectomy) are treated with estrogen. Women with natural menopause have been treated with both estrogen and estrogen + progestin for symptomatic relief of hot flashes, night sweats, mood swings, etc.

THE WYETH STORY: A VERY GENERAL NARRATIVE

How Wyeth created a demand for its hormone therapy products

Menopause was first described in the published medical literature in the late 1800's. The dawn of the 20th century saw a growing quest for treatment to maintain the youthfulness, sexual health and vitality of women. As awareness of the effects of menopause increased, so did the desire for a magic "cure". Wyeth saw the opportunity to capitalize on this trend by developing a blockbuster drug. In 1942, Wyeth's predecessor Ayerst received approval for the patent of Premarin, a mix of estrogens extracted from the urine of pregnant mares. Ayerst received FDA approval to market Premarin the same year.

Premarin was approved initially as a "replacement" therapy, to "replace" the estrogens that began to disappear from a woman's body. In other words, the FDA approved Premarin only to relieve menopausal symptoms like hot flashes, vaginal atrophy and osteoporosis. Nevertheless, Wyeth boasted additional benefits for Premarin (and later Prempro) beyond FDA-approved uses. It is a violation of FDA regulations for drug companies to promote their products for off-label uses. As described below, in its zeal to monopolize the enormous menopause market, Wyeth shamelessly broke the law.

Wyeth created a demand for Premarin by overpromoting it through the popular press.

In 1962, Dr. Robert Wilson, a New York gynecologist, wrote an article published in the *Journal of the American Medical Association (JAMA)*, which claimed that taking estrogen during menopause *reduces* breast and genital cancers. Later, in 1966, Dr. Wilson authored a bestseller entitled *Feminine Forever*. Wilson denied that menopause is a phase of life. Instead, he characterized it as a disease. Wilson claimed that estrogen was the cure for "the tragedy of women." Menopause, he declared, caused women to lose their youthful appearance and lose their sexuality as if they were castrated. Not only was menopause curable, but it was "completely preventable" if women would take estrogen before entering menopause and continuing for the rest of their lives. The following quotes illustrate how Wilson's book sold the estrogen concept to naïve physicians and a susceptible generation of women:

- * "Multiplied by millions, [the menopausal woman] is a focus of bitterness and discontent in the whole fabric of our civilization."
- * "To watch a pleasant energetic woman turn into a dull-minded but sharp-tongued caricature of her former self is one of the saddest of human spectacles."
- * "[With hormone medications,] breasts and genital organs will not shrivel. Such women will be

much more pleasant to live with and will not become dull and unattractive.”

Dr. Wilson did not divulge in his book that Wyeth paid him to write *Feminine Forever*. Wyeth also paid Wilson to lecture to women’s groups about his book and poured thousands of dollars into his research. Wyeth purchased thousands of copies of the book – so many copies that *Feminine Forever* made it onto the Bestseller List. Wyeth’s sales force then distributed copies to physicians throughout the country. As a result, Wyeth’s sales of Premarin quadrupled.

Wyeth saw enormous profit in the notion that it could convince doctors to prescribe Premarin to every middle-aged woman in civilized society for the rest of their lives. Wyeth ran ads in medical journals urging physicians, “Treat her with Premarin. Keep her on Premarin.”

In 1975, Wyeth ran an advertisement in *JAMA*, claiming that Premarin would relieve “tension, irritability, headaches, undue fatigue, depression and insomnia” caused by declining hormone levels. In bold large, letters, Wyeth advised doctors, “Almost any tranquilizer will calm her down ...but at her age, estrogen may be what she really needs.”

Wyeth also targeted popular women’s magazines by placing objective looking “articles” about menopause. For instance, a piece published in *Harper’s Bazaar* claimed, “There doesn’t seem to be a sexy thing estrogen can’t and won’t do to keep you flirtatiously feminine for the rest of your days ...a real package deal that spruces up your vagina. Prevalent medical opinion is that the safety and benefits of ERT have been convincingly demonstrated.”

Wyeth’s plan worked. By the mid-1970s, doctors wrote more than 30 million prescriptions for Premarin every year. Over time, Premarin became the fifth most frequently prescribed drug in the United States.

Despite cancer side effects, Wyeth found new ways to keep promoting Premarin.

Just as Wyeth’s Premarin profits peaked, new studies showed a link between menopausal use of estrogen and endometrial (uterine) cancer. The first study appeared in the *New England Journal of Medicine* in 1976. As a result, physicians stopped prescribing Premarin for women, except those who had hysterectomies and therefore were not at risk for endometrial cancer. Estrogen sales plummeted. By 1979, the only FDA approved use of estrogen was for treatment of hot flashes and vaginal dryness.

Wyeth needed a new justification for women to keep taking Premarin. In 1980, Wyeth found it: An article by Dr. Don Gambrell published in *Obstetrics and Gynecology* reported that adding progestin to estrogen led to a *decline* in endometrial cancer. Thus, Wyeth, through its sales representatives, convinced doctors that adding progestin (MPA) to estrogen hormone therapy would protect the uterus from cancer.

In 1985, Wyeth developed another marketing spin to promote hormone therapy drugs: HRT could prevent osteoporosis, or bone loss. But, in order to generate sales, Wyeth had to

recast osteoporosis into a terrible, debilitating disease that targeted and struck down menopausal women. Accordingly, Wyeth hired a public relations firm to create public awareness of osteoporosis. In the process, Wyeth learned that 77% of women had never even heard of osteoporosis. Wyeth jumped at the chance to turn ignorance into profits. Wyeth embarked on a major PR campaign, including funding a National Osteoporosis Week, and later, the National Osteoporosis Foundation. Wyeth cleverly used these organizations to promote Premarin as a cure for bone loss in older women.

At around the same time, Wyeth also wanted to claim that HRT prevented cardiovascular disease. Wyeth knew that if it could make the claim that its drugs protected against the biggest killer of all, it could promote Premarin as a recommended treatment for *all* women. In 1985, the Nurses Health Study (NHS) was published. The NHS was a huge study of nearly 122,000 women nurses. The study suggested that women using HI were at a lower risk of developing coronary heart disease. Wyeth asserted that the results proved Wyeth's claim that HRT prevented cardiovascular disease. Wyeth used the NHS as another promotion gimmick to boost sales of Premarin and MPA. Wyeth overstated the study's findings. Wyeth ignored the study's numerous limitations. For instance, the study was not randomized. Moreover, the nurses in the study were more educated and compliant as patients than the population at large. However, those obvious shortcomings did not prevent Wyeth from exploiting the NHS for its own gain.

Wyeth made wild claims about benefits of its HRT drugs without scientific support

By the late 1990s, Wyeth touted Prempro as effective treatment for myriad diseases, including Alzheimer's, vision problems, tooth loss, heart disease and colon cancer. Yet the FDA had not approved Prempro for treatment of any of these conditions. Wyeth's promotional tactics in making these dazzling but unwarranted claims included scaring women about menopause. For example, in 1999, Wyeth distributed a brochure to women through the waiting rooms of doctors' offices, which read "Menopause isn't gone in a flash – its debilitating consequences can affect the rest of your life."

Wyeth hired model Lauren Hutton to boast estrogen's cosmetic effects, claiming the drug was her Number 1 secret: "It's good for your moods, it's good for your skin. If I had to choose between all my creams and makeup for feeling and looking good, I'd take the estrogen."

Wyeth promoted long-term use but understated the side effects

Wyeth also pushed HRT for *long-term* use to prevent an ever-increasing assortment of diseases with little or no scientific justification. In its advertisements and promotional materials, Wyeth emphasized HRT's "long-term health protection" and urged physicians to prescribe it indefinitely, even after short-term menopause symptoms, such as hot flashes, had subsided. Meanwhile, in its advertisements, Wyeth glossed over the risks associated with HRT. Most disturbing were "seminar" programs Wyeth created for consumers in the early 1990s. These videos used a doctor-spokesperson to emphasize long-term benefits of HRT and to advise patients that the benefits far outweighed cancer risks.

Wyeth needed a new HRT drug to make up for the loss of Premarin's patent

Premarin's patent protection would end in 1995. Faced with the threat of a shrinking market, Wyeth developed a single combination therapy pill that would combine Premarin with progestin (MPA). Before then, Wyeth had little success marketing Cycrin, its own brand of MPA compared with its better-known competitor Provera, manufactured by Pfizer. By combining both Premarin and MPA into a single pill offered convenience and guaranteed a new long patent life for Wyeth's HI product line.

Prempro's big clinical study goes South on Wyeth

Soon after introducing Prempro, Wyeth began funding a 4-year heart disease prevention trial known as HERS (Heart and Estrogen/Progestin Replacement Study). Wyeth had high hopes that HERS would show that HRT prevents heart disease in high-risk women. If so, Wyeth could then receive FDA approval to market Preinpro for heart disease. In 1998, Wyeth's hopes were dashed. That year, the HERS investigators reported that HRT did *not* reduce the rate of coronary adverse events in women with pre-existing heart disease. The fate of Prempro for treatment of heart disease lay in another study already underway, known as WHI (Women's Health Initiative Study).

While Wyeth waited for the WHI study researchers to collect their data and reach their conclusions, the company continued to exploit the menopause market through overzealous HRT promotion. In its brochures, Wyeth assured consumers with testimonials that Prempro was "time tested" and had a successful safety track records. However, buried in fine print were warnings about numerous serious side effects.

WHI study revealed that estrogen therapy causes disease instead of preventing it

The Women's Health Initiative is a group focused on defining the risks and benefits of potential treatments to reduce the incidence of heart disease, breast and colorectal cancer and fractures in post-menopausal women. Between 1993 and 1998, the WHI enrolled 161,809 post-menopausal women from 50 to 79 years old in a set of clinical trials and an observational study at 40 clinical centers in the United States. One arm of the study was done by the National Heart, Lung and Blood Institute (NHLBI), which was a sub-organization of the prestigious National Institutes of Health (NIH).

The NHLBI arm of the Will study consisted of 16,608 women ages 50 to 79 with a uterus. They were randomly assigned to a dose of either placebo or the combination of estrogen plus progestin (*i.e.*, combination HRT) in the form of Wyeth's drug Prempro. The study's objective was to look at the effect of HRT on the prevention of heart disease and hip fractures, as well as any change in risk for breast and colon cancer over the 5-year study period.

On May 31, 2002, the study's Data Safety and Monitoring Board - which met regularly to review

results and patient safety – determined that the number of cases of invasive breast cancer in the Prempro group had risen to the point of showing an increased risk. The DSMB recommended stopping the trial based on the finding a heightened breast cancer risk, supported by the evidence that overall health risks exceeded any benefits. In July, patients were notified of the results and told to discontinue the medications.

The results of the WHI study were published in *JAMA* in July, 2002. The results showed not only an increased risk of breast cancer, but an elevated risk of cardiovascular disease and heart attacks, the very conditions Wyeth claimed its HF drugs would prevent. Compared to placebo, HRT was associated with the following:

- *41% increase in strokes.
- *29% increase in heart attacks
- *100% increase – a doubling of risk – of venous thromboembolism (blood clots)
- *22% increase in total cardiovascular disease
- *26% increase in breast cancer
- *37% reduction in cases of colorectal cancer
- *33% reduction in hip fractures

The study concluded that over the long-term, combination HRT should not be used or continued for the primary prevention of coronary heart disease. The authors stated that the risk was too high a price to pay for any benefits such as reduction of the risk of hip fractures. Dr. Roussow, the lead author, pointed out that “even small individual risks over time, and on a population-side basis, add up to tens of thousands of these serious adverse health events.”

A study by the NCI found that Estrogen-only therapy causes ovarian cancer

In July 2002, just days after the WHI results were reported, *JAMA* published the results of a study by the National Cancer Institute, which found that women who took estrogen therapy were more likely to develop deadly ovarian cancer than those who didn't. The NCI study followed 44,241 women for 19 years who took estrogen only and found that they had a 60% higher risk of ovarian cancer. The risk increased proportionately the longer women took estrogen. Women on estrogen for 10-19 years had an 80% higher risk, and those on the drug for 20 years or more were more than 3 times as likely to develop ovarian cancer.

Dr. James Lacey, the lead author, expressed concerns about the public health impact of estrogen therapy. His findings translated into one or two additional ovarian cancers each year per 10,000 women taking estrogen alone. Indeed, in 2000, some 8 million women took Premarin. Based on the Lacey study, Premarin is responsible for up to 1,600 additional ovarian cancers in 2000 alone.

A year later, the Will Prempro study group published more findings, which echoed the findings of Dr. Lacey's NCI study. *JAMA* reported in October 2003 that the combination of estrogen and progesterone was associated with a 58% increase in ovarian cancers.

The WHI and NCI studies generated unprecedented media attention and research

Never before had hormone therapy created so much attention until the results of the WHI and NCI became public. The two studies received enormous media coverage. Front-page newspaper headlines, magazine covers and broadcast news programs urgently reported the alarming findings.

For the first time, physicians and researchers were forced to confront the risks versus benefits of hormone therapy for patients. The following two comments are illustrative:

“The reduction in colorectal cancer risk in the Will is intriguing, but the balance of harm versus benefit does not justify any woman beginning or continuing to take estrogen plus progestin for this purpose.” Dr. Leslie Ford, Associate Director for Clinical Research, Division of Cancer Prevention, NCI.

“Quality of life is very, very important . From a heart and breast cancer point of view, the drug should be outlawed. But for hot flashes, there’s nothing better.” Dr. Isaac Schiff, Massachusetts General Hospital.

The publicity that the WHI and NCI studies received also generated new research on the risks and benefits of hormone therapy. As the next section explains, later studies confirmed the findings of WHI and NCI.

Study after study shows that the risks of HRT outweigh its benefits

Beginning in 2002, additional research yielded more evidence that long-term hormone therapy has dangerous side effects and no meaningful upside. Specifically, these studies found that Hi’ increases the risk of breast cancer, heart attacks, bone loss and other conditions. And more studies are currently underway. Below is a summary of the key research:

* WISDOM. The United Kingdom’s Medical Research Council began a prospective study entitled Women’s International Study of Long Duration Oestrogen after Menopause (WISDOM). The study was to follow 22,000 women. Following the WHI study, the Council canceled WISDOM on October 22, 2002, concluding that “[t]here is strong evidence that taking hormone therapy long term increases the risks of some diseases such as breast cancer and decreases the risks of others such as osteoporosis.”

* Li Study (University of Washington). January 2003. *J. Clini. Oncol.* Dr. Li and colleagues conducted a case/control study of a nationwide comprehensive breast cancer registry from 1992 to 1998. The data from the registry have long been available to the public. They found that among older women, hormone receptor negative breast cancers did not increase. But the rate of hormone receptor positive breast tumors *did* increase in older women. The study concluded that HRT is probably responsible for all of the increase in breast cancer in the U.S. since at least

1992.

* Quality of Life Study: *NEJM*, March 17, 2003. This was the same study pool of 16,000 women as the 2002 WHI study. In its follow-up, researchers found that HRT drugs fail to do the very thing women took them for in the first place: to make them feel happier and healthier after menopause. In other words, HRT did not improve the quality of life for menopausal women. In addition, the authors concluded that HRT plays no meaningful role for HRT in treating women without menopausal symptoms. If women do continue with HRT, they should take the *losest possible dose for the shortest possible time*.

* Bone Loss Study: *JAMA*, May 21, 2003. This study examined the efficacy of estrogen + progestin therapy (e.g., Prempro) for prevention of bone loss in elderly women. It included 373 women ages 65 to 90 who had either thinning bones or full-blown osteoporosis. The study compared the effectiveness of HRT to Fosamax (alendronate, a bone-building drug), the combination of Fosamax and HRT, and placebo. The authors concluded that Fosamax alone was more effective than both Fosamax/HRT and placebo.

* Alzheimer's and Dementia: *JAMA*, May 28, 2003. This was a 4-year trial of 4,532 women. Half took Prempro, half took placebo. The study found that estrogen + progestin doubled the risk of dementia for women who started HRT at age 65 or older.

* Mammography Study: *JAMA*, June 25, 2003. This study analyzed additional data from the Will. It found that besides stimulating the growth of breast cancer combination estrogen-progestin therapy makes breast tumors harder to detect, leading to dangerous delays in diagnosis. The report found that breast abnormalities can develop even after *short-term* use. In the same issue, *JALV4* published an editorial by Dr. Peter Gann, a cancer epidemiologist, who stated that the study represents "further compelling evidence against the use of combination estrogen plus progestin hormone therapy."

* Million Women Study: *Lancet*, August 9, 2003. This is an ongoing study of over 1 million women between ages 50 and 64, which will continue to yield valuable research over time. This particular report looked at the data between 1996 and 2001, following women to look for cancer incidence and death. It is the largest study of women to date. Results showed that post-menopausal women using combination estrogen/progestin therapy were *twice* as likely to develop breast cancer as non-users – a 100% increased risk. The risk went up with the duration of use. The study confirms the findings of Will.

* Swiss Breast Cancer Study: *Int. J. Cancer*, May 10, 2003. Researchers analyzed the histology of 6,647 breast cancers in the Geneva breast cancer registry to see if there was an increasing trend of breast cancers. The study found a significant 7-fold increase in lobular breast cancers, but only in post-menopausal women. The increase could not be explained by more widespread use of mammography. The authors attributed the rising rate of lobular cancers to hormone therapy and found that the trend was similar to Dr. Li's findings in the University of Washington study.

HRT also causes other diseases, including autoimmune diseases

Still more studies suggest that hormone therapy can lead to gallbladder cancer, arthritis, asthma, hearing loss, and autoimmune disease, including lupus. Wyeth had never warned of these diseases in its labeling.

- * Lupus: *Ann. Internal Med*, March 1995. This prospective study of 69,435 women found a 2.7 -fold increased risk of systemic lupus erythematosus with estrogen therapy after 5 to 10 years. The risk rose to a 3.5-fold increased risk after 11 or more years.
- * Arthritis: *Health Records*, Autumn 1999. The study found a two-fold increased risk of incident arthritis in women over 38 who had used UT for five years or longer.
- * Asthma: *Arch. Intern Med.*, 2004. Current users of estrogen/progestin therapy were more than twice as likely as non-users to develop asthma.
- * Gallbladder: *Int. J. Cancer*, 2003. Women over 45 years on HRT were over 3 times as likely to develop gallbladder cancer than non-users. The risk appears to increase with duration of use. (note –it is not clear whether HI use consisted of EI or combination use).

Wyeth changed its HRT label and reversed its “long-term use” marketing strategy

After the WHI, NCI and other studies became public, it was clear that the labeling information Wyeth provided to consumers was inaccurate and misleading. Wyeth changed its warning label on Premarin and Prempro during the last week of August, 2002 to reflect the results of the July, 2002 Will and NCI studies.

Before the August 2002 label change, Premarin contained no warning or mention whatsoever of ovarian cancer.

There were never any warnings in the Premarin or Prempro labels for autoimmune disease, arthritis, dementia, hearing loss or gall bladder cancer.

Before August 2002, the Prempro warning labels were also inadequate and misleading. For example, the label stated a risk of breast cancer with conjugated estrogens (i.e., the Premarin component of Prempro), but then indicated that combining the progestin component did not raise the risk of breast cancer: “The overall incidence of breast cancer does not exceed that expected in the general population.” The WHI study plainly reveals that this warning is false and was known or should have been known by Wyeth for decades.

The Prempro warnings also understated the risk of two thromboembolic disorders: pulmonary embolisms and blood clots. Wyeth also downplayed the risks of cardiovascular disease and strokes. The “precautions” sections stated, “The effects of estrogen replacement

therapy on the risk of cardiovascular disease have not been adequately studied.” Nevertheless, Wyeth has long promoted the supposed benefits of long-term hormone therapy for cardiovascular disease.

On January 6, 2003, Wyeth finally abandoned its long-standing marketing strategy of promoting long-term use of Premarin and Prempro. Wyeth issued a “Dear Doctor” letter to healthcare professionals, explaining that it would adopt new labeling for its HI drugs as a result of the WHI findings. According to the letter, Wyeth’s new HRT labels would contain a “black box” warning:

“...[E]strogens and estrogens plus progestin therapies should not be used for prevention of cardiovascular disease ... The boxed warning also includes information [stating that because of the WHI study] ... estrogens and estrogens plus progestin *should be prescribed for the shortest duration consistent with treatment goals.*”

In early June, 2003, Wyeth launched its new marketing and public relations campaign with full-page advertisements placed in newspapers worldwide, titled “A message from Wyeth.” The advertisement stated hormone therapy should be taken for *the shortest duration at the lowest effective dose*. By then, Wyeth was marketing a low dose form of Premarin and Prempro pursuant to FDA’s request to do so.