

**WILLIAMS CUKER BEREZOFSKY**

Woodland Falls Corporate Park  
210 Lake Drive East, Suite 101  
Cherry Hill, New Jersey 08002-1163  
856-667-0500

*Attorneys for Plaintiffs*

---

ELLEN DEUTSCH, and her husband,	:	SUPERIOR COURT OF NEW JERSEY
DAVID N. DEUTSCH,	:	LAW DIVISION
	:	MIDDLESEX COUNTY
Plaintiffs,	:	
	:	Docket No. L-0998-06 MT
-vs-	:	Case No. 266 - HT Litigation
	:	
WYETH, INC.; WYETH	:	
PHARMACEUTICALS, INC., et al,	:	Civil Action
	:	
Defendants.	:	

---

---

PLAINTIFFS' PRETRIAL BRIEF

---

WILLIAMS CUKER BEREZOFSKY  
210 Lake Drive East, Suite 101  
Cherry Hill, New Jersey 08002  
(856) 667-0500

Attorneys for Plaintiffs

Kevin Haverty, Esq.  
On the Brief

## PRELIMINARY STATEMENT

This case involves the failure to properly warn about the risks of breast cancer posed by long-term use of Prempro. Plaintiffs allege that the warnings on Premarin and Prempro before publication of the results of the Women's Health Initiative (WHI) study did not provide an accurate assessment of the breast cancer risk because Wyeth neither tested nor studied the product appropriately in order to determine the risk associated with its use. Instead Wyeth aggressively promoted the product for long-term use without knowing what the long-term risks were. The effect of such studies, had they been done when combination therapy first began to be used in the late 1970s, would have resulted in the label that is currently on the product which strongly warns of the risk of invasive breast cancer, cautions doctors and patients to use the product only as a last resort and then only at the lowest dosage for the shortest possible time. The effectiveness of the current label is vividly demonstrated by the significant and sustained decrease in the number of women using Prempro which has led to a substantial and unprecedented decrease in the incidence of breast cancer in post-menopausal women. We know now that combination HRT with the synthetic progestin MPA has caused more than 150,000 cases of breast cancer in the USA alone in the past 25 years; the tragedy of this case is that proper studies by a responsible drug company would have prevented almost all of those breast cancers, including that of Mrs. Deutsch.

## **LIABILITY**

### 1. Failure To Warn

This is a pharmaceutical products liability action involving Wyeth's hormone replacement therapy product Premarin (used with Provera) and Prempro. Prempro, first introduced in late 1995, was the first single-pill combination estrogen/progestin hormone replacement therapy medication. Its approved indications, then and now, are for the relief of menopausal vasomotor symptoms (hot flashes), the treatment of vaginal atrophy, and osteoporosis prevention. The use of a combination of estrogen and progestin for the treatment of menopausal symptoms in un-hysterectomized women has been common practice since the late 1970's following reports of an increased incidence of uterine cancers associated with that the use of estrogen alone. It was theorized that the addition of a synthetic progestin to "oppose" the estrogen would mitigate the effects of continuous exposure to estrogen on the risk of uterine cancer.

The uterine cancer epidemic held several lessons for makers of hormone drugs:

1. It was a signal that menopausal hormone pills could cause cancer in hormone sensitive organs;
2. The signal was confirmed to be real by case control studies done on cancer registries, which are a type of study that can be done very quickly and inexpensively.
3. Not all types of uterine cancer was caused by the hormone pills: only the subtypes of uterine cancer that were hormone dependent, estrogen fed, were on the rise in women using Premarin.

4. The cancer risk fell quickly and sharply once women stopped taking the hormone pills, agreed by all in the literature at the time to be a “promotion” effect rather than a cancer “initiation” effect.

However, even in the light of the uterine cancer crisis, Wyeth, the leading manufacturer of hormone drugs never conducted any clinical trials or observational studies with a primary endpoint of addressing whether the new combination drugs would cause cancer in the next most hormone sensitive organ—a woman’s breast. Plaintiffs’ expert Cheryl Blume, Ph.D., explained that instead of testing or doing studies concomitant with the increasing use of Provera in combination with estrogen, “Wyeth tried on multiple occasions to get NDA approval for combination therapy with Premarin and MPA based solely on data gathered from the literature.”

According to Dr. Blume:

There were no pivotal randomized clinical studies supporting Wyeth’s products until the mid 1990's, and even then only one clinical trial was conducted. In 1994, Wyeth received NDA approval for combination therapy with estrogen and MPA based on the data generated in a trial designed to compare frequencies of endometrial hyperplasia in post menopausal women receiving conjugated estrogens or the combination of conjugated estrogens and MPA. Notwithstanding the relatively small patient numbers receiving combination therapy (~1000), a breast cancer signal was observed when 6 women were found to develop breast cancer on study.

Based on this data, the FDA asked Wyeth to commit to a Phase IV study to specifically evaluate breast cancer risks with the combination therapy. Wyeth never conducted this evaluation and instead waited for WHI to reconfirm (in 2002) the breast cancer signal that had been noted almost a decade earlier with Prempro therapy.

Exhibit 6 at 20.

To say that the pre-WHI Premarin and Prempro labels are radically different than the post-WHI labeling would be a massive understatement; it is indeed a tale of two labels. Consider the discussion of breast cancer. While the initial “warnings” note that there are “[s]ome studies” that suggest a “possible” risk, they go on to say, in the very next line, that “[t]he majority of studies” show no risk. The labels further downplay any causal link by indicating that some estrogen studies (as distinct from combination hormone therapy studies) have reported a “moderately increased risk” from estrogen which the labels quantify as a relative risk on the order of 1.3 to 2.0.

[T]he breast cancer warning that did appear in the Prempro label provided only an estrogen therapy relative risk statistic, the statistic was inaccurate and did not include the true risk range, did not include risk statistics for combination therapy and misrepresented Wyeth’s data from the Prempro pivotal trial. Further, Wyeth consistently emphasized only the one minimizing and reassuring statement from the label: **“the majority of studies, however, have not shown an association in women who have ever used estrogen replacement therapy.”** The Prempro label did not include important risk information such as the increase in a woman’s risk level if she is lean, overweight or had a family history of breast cancer. The Prempro label also did not include a warning that use of combination therapy could cause pre-existing breast abnormalities or dormant masses to grow or develop into cancer and that combination therapy could cause hormone receptor positive tumors as well as rare cancer tumors (such as lobular or tubular). Lastly, the Prempro label did not warn women that combination therapy could aggravate or escalate the growth of breast cancer after a short period of exposure to the drugs and that even short term use carried significant risk. The label also did not warn that a woman’s risk increased with duration of use and that long-term use carried with it excess risk.

As Dr. Blume noted, the label’s statement that **“the effect of added progestins is “unknown””** although a “moderate risk has been reported” at a minimum “misrepresented Wyeth’s data from the Prempro pivotal trial.” And the very next passage neutralizes what

minimal caution this hapless statement might have provided by reporting that a one-year trial had reported virtually no risk. Aside from the fact that the labels actually misstate the study's finding, one year is an insufficient time period to evaluate or even quantify a risk—particularly a cancer risk. More significantly, the final sentence of the section states: **“The overall incidence of breast cancer in this [one year] clinical trial does not exceed that expected in the general population.”** Like the earlier statement about the “majority of studies” showing there is nothing to worry about, this statement nullifies the remainder of the “warning” by implying that those who take hormone therapy have no greater incidence of breast cancer than those who don't. These “warnings” are nothing of the sort and far from even close to adequate. Yet, as will be shown at trial, they contain precisely the language and concepts that informed the thinking of Ellen Deutsch's prescribers, and Ellen Deutsch, before WHI.

The current label is a portrait in stark contrast. The newer label contains a nearly full-page “black box” warning at the very start. The discussion of breast cancer does not even remotely resemble that of the older labels. Gone is Wyeth's previous claim that the “majority of studies” suggest no link. Gone is Wyeth's claim that the risk is merely “possible” or “moderate.” Gone is Wyeth's claim that the effect of added progestins is unknown. Gone is Wyeth's claim that the incidence of breast cancer among users is no greater than that of the general population. And gone is any reference to the meaningless one year trial Wyeth referenced before. Included, by comparison is an extensive discussion of the WHI study as well as others, such as the Million Women Study from Great Britain.

Perhaps most significantly, and apropos of the issue before the court, Wyeth acknowledges in the current labels that hormone therapy should be used very cautiously and, even then, in the lowest effective dose for the shortest reasonable duration saying: “Use of estrogens

alone or in combination with a progestin, should be with the lowest effective doses for the shortest duration consistent with treatment goals and risks for the individual woman. According to the label, the “lowest effective dose” for the treatment of vasomotor symptoms of menopause (the indication for which Prempro was prescribed to Mrs. Deutsch) is 0.3 milligrams of estrogen with 1.5 milligrams of progestin. This is in sharp contrast to the high doses of 0.625 milligrams estrogen and 5 milligrams progestin Mrs. Deutsch was prescribed for a prolonged period of time.<sup>1</sup>

As Dr. Blume opined:

The current [2005] Premarin and Prempro labels finally provide adequate information concerning the risks associated with Premarin and Prempro and Premphase treatment. If Wyeth had conducted the appropriate studies, this information would have been provided to physicians more than a decade earlier. In addition, the process by which these labels evolved was protracted and intentional. For years, Wyeth disseminated information that obscured and hid the issues.

Wyeth failed to reveal the morbidity and mortality risks associated with its hormone therapy drugs. For example, the authors of the WHI study calculated that the absolute excess risks per 10,000 person-years attributable to estrogen plus progestin were 7 more CHD events, 8 more strokes, 8 more pulmonary embolisms, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The authors of the Million Women Study estimated that 10 years’ use of HRT would result in 5 additional breast cancers per 1000 uses of estrogen-only preparations and 19 additional cancers per 1000 users of estrogen–progestagen combinations. They further estimate that use of HRT by women aged 50-64 years in the UK over the preceding decade had resulted in an estimated 20,000 extra breast cancers, 15,000 of which were associated with estrogen-progestagen combination therapy. By

---

<sup>1</sup>

Mrs. Deutsch was started on the 0.625/5 mg regime and remained at that dosage for some indeterminate number of years. In April, 2000 there is a note that progestin component was reduced to 2.5 mgs.

easy mathematical translation to this country, the Million Woman Study shows that there were likely more than 100,000 unnecessary breast cancers associated with hormone therapy use.

It is this label that plaintiffs have consistently argued contains the warnings defendants were obliged to provide Ellen Deutsch and her physicians while they were treating her.

### **CAUSATION**

Ellen Deutsch was started on Premarin in combination with Provera in early 1995 for treatment of menopausal vasomotor symptoms (hot flashes). In August, 1996 she was switched to the then relatively new single pill combination therapy Prempro. She remained on Prempro for more another six years until April, 2002 when she was diagnosed with metastatic cancer of unknown primary origin.

In December, 2001, Mrs. Deustch fell and injured her leg. Due to ongoing complaints of pain, she began to treat with an orthopedist and chiropractor. Nevertheless she continued to experience a worsening of her symptoms despite treatment and in late February, 2002, her primary care physician ordered an MRI of the spine. The MRI revealed multiple lesions suspicious for metastasis. On April 9, 2002 she underwent a biopsy of the sacral mass described in the MRI. That biopsy was positive for metastatic disease but was unable to definitively identify a primary source. She was thereafter referred to an orthopedic oncologist at Mt. Sinai Medical Center in New York who recommended treatment by a medical oncologist. On April 24, 2002, Mrs Deutsch was seen by Stuart Leitner, M.D., a medical oncologist who ordered additional testing including a mammogram as well as testing for the hormone receptor status of the sacral biopsy tissue. Two days later Mrs. Deutsch was seen by Michelle O'Shea, M.D., a breast surgeon who performed a biopsy of a suspicious mass in the breast. On May 3, 2002, Dr. Leitner advised Mrs. Deutsch that the testing confirmed that she had primary breast cancer which

had metastasized to the her bones in multiple locations. Significantly, hormone receptor testing revealed a strongly estrogen-positive tumor (> 90%) which was also progestin positive (40%).<sup>2</sup>

#### A. GENERAL CAUSATION

In the mid-1970's a sharp increase in the incidence of uterine cancers was reported among post-menopausal women taking estrogen. When this information was reported, the rate of use of estrogens—which had been steadily climbing for years—fell sharply. Follow up epidemiological studies found that the rise in certain subtypes of uterine cancers, namely cancers of the hormone sensitive endometrium neatly tracked the rise in use and likewise there was a steep decline in cancer incidence which tracked the steep decrease in use of the drug. Based upon the medical knowledge that effect of estrogen is to promote proliferation of hormone-sensitive cells, it was proposed that the addition of a progestin to the therapy to “oppose” the proliferative effects of estrogen would reduce the risk of endometrial cancer. Beginning in the late 1970s standard therapy for un-hysterectomized post-menopausal women was to combine a progestin with an estrogen to offset the uterine cancer risk. No studies of the long-term effects of this regimen were undertaken or even proposed by the companies producing, promoting and selling the drugs being used. Tragically, Wyeth never looked at any of the available cancer registries, despite the surge in sales of Premarin in the late 1970s due to the purported “solution” of the uterine cancer problem of adding a second hormone to the mix.

Based upon the model of the uterine cancer epidemic, the proposed mechanism by which combination hormone therapy causes cancers is by “promoting” already abnormal—but not

---

<sup>2</sup>

Of note is the fact that the progesterone receptors decreased from 40% to 10% following the cessation of HRT further supporting a drug effect on the tumor.

cancerous—cells to become cancerous. This “promotion” model is further supported by increased breast density seen on mammograms in women taking combination therapy as well as the recent findings of two studies which described a sharp decrease in the incidence of hormone-dependent cancers seen immediately following the publication of the results of the Women’s Health Initiative which led to a significant and prolonged decrease in the use of HRT. Additionally, the promotion mechanism is further supported by the response seen in women with hormone-dependent cancers treated with anti-hormone therapy. Moreover, it is well known that menopausal women frequently have abnormal cells in their breasts as they enter menopause which are highly dependent on hormones for growth and survival. Menopause (and the cessation of natural hormones) would stop the growth of such hormone dependent abnormal cells. However, feeding such abnormal cells with combination hormone therapy causes such cells to grow and develop into cancer.

#### B. SPECIFIC CAUSATION

Ellen Deutsch took combination hormone replacement therapy for more than seven years beginning in early 1995. According to the WHI, the risk of breast cancer begins to rise after just under 5 years of use with a relative risk of 3.08 for women who used combination therapy for at least seven years. Additionally, plaintiffs’ expert radiologist Cecilia Brennecke, M.D. has opined that the density of Mrs. Deutsch’s breasts began to decrease consistent with her entry into menopause and then increased to at least her pre-menopausal levels following the initiation of continuous, combined therapy with Prempro. Perhaps more significantly, Dr. Brennecke opined that Ellen Deutsch’s breast density again began to decrease after she went off HRT and began therapy with the anti-estrogen drug Femara.

Richard Hirschman, M.D., a medical oncologist and one of plaintiffs' expert witnesses opined that:

- All indications—particularly the findings that her breast and bone metastasis were EP receptor positive. . .—are that her breast tissue was extremely sensitive to the carcinogenic effects of the hormone therapy drugs . . . she ingested, which caused increased cell proliferation, increased density, and decreased involution in her breast.
- That her breast cancer was hormone-induced and hormone-dependent is further evidenced by the success achieved to date of Femara, an anti-estrogen drug, to stabilize the course of her bone metastasis.
- Exogenous sources of hormone therapy were necessary to promote the breast cancer from which her injuries and shortened life expectancy flow, as the vasomotor menopausal symptoms she suffered signaled that her endogenous estrogen levels were low.
- Mrs. Deutsch's breast cancer was caused by long-term use of combination hormone therapy. Several factors strengthen this conclusion, including her longstanding use combination hormone therapy, the fact that her cancer was EP receptor positive . . . and the fact that her breast tissue and breast tumor manifested sensitivity to exogenous hormone therapy.

## II. DAMAGES

Ellen Deutsch was diagnosed with metastatic breast cancer on May 3, 2002. In addition to the primary tumor in the breast for which she underwent lumpectomy on May , 2001, bone metastasis was found in multiple discreet locations including the sacrum, the right iliac bone, the spine at T11, the clavicle, the right parietal bone and the temporomandibular joint. She is being treated with Femara and Zometa (for bone metastasis), the latter of which she received monthly until recently when the regimen was changed to quarterly.

Despite the regression and stabilization of her metastatic disease her prognosis remains poor. According to Dr. Hirschman—who examined her—“[h]er chance of surviving 10 years is less than 10 percent, and it is likely that her pain and suffering from the bone metastasis will increase,

and her condition will deteriorate over the near term.” In a supplemental report, Dr. Hirschman elaborated further saying that:

Mrs. Deutsch is in a remission induced by anti-estrogen therapy (Femara). Periods of remission typically last 2 to 3 years. To some extent, Mrs. Deutsch is an outlier for being able to remain in remission beyond 3 years. However, it is inevitable that this therapy will fail and she will rapidly decline from her present state of disability. The decline will inevitably include more bone involvement, chemotherapy, radiation, stronger narcotics, and the need for part time nursing care progressing to full time nursing care, and then palliative care, including full time hospice care or its equivalent. The side effects of these therapies include nausea, hair loss, vomiting, muscle pain, bone pain, neurologic side effects and a diminished ability to care for oneself.

Based upon Dr. Hirschman’s assessment of Mrs. Deutsch’s prognosis and expected pattern of disease progression, plaintiffs’ life care planner Lorraine Buchanan, R.N., M.S.N., C.R.R.N. estimated the costs of this end stage medical care at a net present value of approximately \$471,000. Additionally, the costs of medical treatment to date is approximately \$245,000.

At the time of her diagnosis with metastatic breast cancer, Ellen Deutsch was 55 years old with a life expectancy of 23.85 years. She has been married to David Deutsch for 37 years and they have three adult children.

#### LEGAL ARGUMENT

Drug manufacturers have a duty to warn consumers of the risks of their drugs. In Feldman v. Lederle Laboratories, Inc., 97 N.J. 429 (1984), the New Jersey Supreme Court declined to categorically hold that “all prescription drugs that are unsafe are unavoidably so,” and thus immune from claims in strict liability. Instead, the court noted that

[W]ith those [unavoidably unsafe] products, the determination of liability may be achieved more appropriately through an evaluation of the adequacy of the warnings. Thus a manufacturer who knows or should know of the danger or side effects of a product is not relieved of its duty to warn. Rather . . . it is only the unavoidably unsafe product “accompanied by a proper warning” that is not defective.

Id. at 447 (quoting O’Brien v. Muskin Corp., 94 N.J. 169 (1983)) (emphasis in original).

A proper, or adequate warning “means a warning adequately communicated to make the product safe for the intended use. Adequately communicated means to provide an appropriate method for bringing the dangers or hazards to the attention of the person who will be using the product for its intended use.” Model Jury Charges - Civil § 5.34B. A product which does not contain an adequate warning about its risks is defective. N.J.S.A. 2A:58C-2.

The risks which a manufacturer must warn about are those which are known or reasonably knowable either at the time of manufacture or which are discovered after the product leaves the manufacturer’s control N.J.S.A. 2A:58C-4. However, in a failure to warn case, the failure to test, which testing may have revealed the risk or danger, may be evidential of the inadequacy of a warning. Green v. General Motors Corp., 310 N.J. Super. 507, 530 n.13 (App. Div.), certif. denied, 156 N.J. 381 (1998).

In this case, it is alleged that the breast cancer warnings on Wyeth’s Prempro product were inadequate as they failed to accurately convey the actual risks of the product. Further, the full extent of the risks could have been known to Wyeth if Wyeth had undertaken studies or done testing of combination hormone replacement therapy. There were multiple and varied types of studies which could have been done 20 years ago which would have revealed the risk uncovered by the Women’s Health Initiative and subsequent studies and led to the labeling currently on the product. Moreover, Wyeth promoted the product for long-term use without studying or testing

the long-term risks associated with such risks. Wyeth's failure to test, particularly while it aggressively promoted the product for long-term use resulted in an inadequate warning and the communication of misleading information to consumers and prescribes.

While generally a drug manufacturer may discharge its duty to warn by providing a warning to the physician—the so-called “learned intermediary,” Nomura v. Schneider, 114 N.J. 550 (1989), the doctrine does not apply where a drug manufacturer has a direct duty to warn a patient, id. or where the reasons for application of the learned intermediary doctrine do not apply as where a manufacturer markets directly to consumers. Perez v. Wyeth Laboratories, Inc., 161 N.J. 1, 4 (1999) (“when mass marketing of prescription drugs seeks to influence a patient’s choice of a drug, a pharmaceutical manufacturer that makes direct claims to consumers for the efficacy of its product should not be unqualifiedly relieved of a duty to provide proper warnings of the dangers or side effects of the product”). 161 N.J. at 4.

Indeed, as the Court in Perez observed, the learned intermediary doctrine arose out of a time when

Pharmaceutical manufacturers never advertised their products to patients, but rather directed all sales efforts at physicians. In this comforting setting, the law created an exception to the traditional duty of manufacturers to warn consumers directly of risks associated with the product as long as they warned health-care providers of those risks.

For good or ill, that has all changed. Medical services are in large measure provided by managed care organizations. Medicines are purchased in the pharmacy department of supermarkets and often paid for by third-party providers. Drug manufacturers now directly advertise products to consumers on the radio, television, the Internet, billboards on public transportation, and in magazines.

Id.

Thus, the Court concluded that

When a patient is the target of direct marketing, one would think, at a minimum, that the law would require that the patient not be misinformed about the product. It is one thing not to inform a patient about the potential side effects of a product; it is another thing to misinform the patient by deliberately withholding potential side effects while marketing the product as an efficacious solution to a serious health problem. Further when one considers that many of these “life-style” drugs or elective treatments cause significant side effects without any curative effect, increased consumer protection becomes imperative, because these drugs are, by definition, not medically necessary.

Id. at 21.

However, in light of our State’s strong embrace of the “prudent patient” standard in medical decision making, see Largely v. Rothman, 110 N.J. 204 (1988) (“it is the prerogative of the patient, not the physician, to determine for himself the direction in which his interests seem to lie”), the focus is not simply on the doctor’s decision making in the face of warnings but also that of the patient. See Brigman v. Wyeth, 384 N.J. 525 (Law Div. 2005) As the court in Brigman put it “[w]hile the law leaves the health care provider free to decline to prescribe the pharmaceutical, the doctrine of informed consent requires the patient to determine whether he or she wishes to take the drug in the first place.” Id. at 541. And by extension, it also applies to the decision to continue a therapy previously initiated. See Matter of Conroy, 98 N.J. 321, 347 (1985) (“a competent patient has the right to decline to have any medical treatment initiated or continued”). The court thus concluded that “Wyeth’s desire to leave the prescribing decision solely in the hands of the learned intermediary runs afoul of New Jersey public policy.” This court correctly held that a plaintiff is entitled to a presumption that she would have heeded a

proper warning and would not have taken the drug as she did if she had been properly warned.

Respectfully submitted,

WILLIAMS CUKER BEREZOFSKY

BY \_\_\_\_\_  
KEVIN HAVERTY

DATED: July 9, 2007