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Menopause, as Brought to You by Big Pharma

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MILLIONS of American women in the 1990s were told they could help their bodies ward off major illness by taking menopausal hormone drugs. Some medical associations said so. Many gynecologists and physicians said so. Respected medical journals said so, too.

Along the way, television commercials positioned hormone drugs as treatments for more than hot flashes and night sweats — just two of the better-known symptoms of menopause, which is technically defined as commencing one year after a woman's last menstrual cycle.

One commercial about estrogen loss by the drug maker Wyeth featured a character named Dr. Heartman in a white coat discussing research into connections between menopause and heart disease, Alzheimer's disease and blindness.

"When considering menopause, consider the entire body of evidence," Dr. Heartman said. "Speak to your doctor about what you can do to help protect your health during and after menopause."

Connie Barton, then a medical office assistant in Peoria, Ill., was one woman who responded to such messages. She says she took Prempro, a hormone drug made by Wyeth, from 1997, when she was 53, until 2002, when she received a diagnosis of breast cancer. As part of her cancer treatment, she had a mastectomy to remove her left breast.

Now Ms. Barton, who said in an interview that she used Prempro in part because her doctor told her it could help prevent heart disease and dementia, is one of more than 13,000 people who have sued Wyeth over the last seven years, claiming in courts across the country that its menopause drugs caused breast cancer and other problems.

The suits also assert, based on recently unsealed court documents, that Wyeth oversold the benefits of menopausal hormones and failed to properly warn of the risks.

In October, a jury in a Pennsylvania state court awarded Ms. Barton $75 million in punitive damages from Wyeth on top of compensatory damages of $3.75 million.

The drug giant Pfizer, which absorbed Wyeth and its hormone drugs in a merger this year, says that Prempro is a safe, federally approved drug that did not cause Ms. Barton's breast cancer. Chris Loder, a Pfizer spokesman, says Wyeth acted responsibly by including a clear warning about a

breast cancer risk on Prempro labels and by updating the warning as new evidence emerged.

Mr. Loder also notes that Pfizer plans to appeal every product-liability case on menopausal drugs it loses, including Ms. Barton's.

While Wyeth has faced periodic complaints about its blockbuster menopause drugs, the latest lawsuits have turned the company's menopausal hormone franchise into the kind of case study dissected at Ivy League business schools. Lawyers have made some documents public in the suits, and The New York Times and the nonprofit Public Library of Science filed successful motions to unseal thousands of documents in July.

To be sure, even some doctors who think hormone therapy has risks say it is the most effective treatment for symptoms directly associated with menopause.

The documents that have surfaced in the Wyeth cases offer a rare glimpse inside the file cabinets and hard drives of a major drug company. And the cases demonstrate the importance of litigation in detailing exactly how drug makers operate their businesses, says Dr. Jerome L. Avorn, a professor of medicine at Harvard Medical School who has written about the subject in The Journal of the American Medical Association.

"The information coming out in litigation helps us understand how a belief in a 'protective benefit' of estrogens on the heart was able to spread like wildfire through the medical community," says Dr. Avorn, who is not involved in the Wyeth litigation.

"Thousands of doctors prescribed the drugs for millions of women on that basis," he says, adding that studies later contradicted the belief. "It will be very interesting to see whether the courts are able to connect the dots and make it clear whether this was a kind of medical ventriloquism on Wyeth's part."

PREMPRO is a combination of Premarin, an estrogen drug derived from the urine of pregnant mares and first approved by the Food and Drug Administration in 1942, with an additional hormone, progestin.

Part of the Premarin saga shows how a drug maker successfully and cannily expanded a franchise whose central ingredient is horse estrogens into a billion-dollar panacea for aging women. Yet several hundred pages of court documents also raise questions about another aspect of Premarin's trajectory: how Wyeth worked over decades to maintain the image and credibility of its hormone drugs even as the products were repeatedly under siege.

Pfizer representatives say court documents paint an unfair picture of Wyeth's practices and that plaintiffs' lawyers have cherry-picked documents for out-of-context comments to sway juries.

Still, the documents offer a snapshot of Wyeth's efforts. Taken together, they depict a company

that over several decades spent tens of millions of dollars on influential physicians, professional medical societies, scientific publications, courses and celebrity ads, inundating doctors and patients with a sea of positive preventive health messages that plaintiffs' lawyers say deflected users' attention from cancer concerns.

Even as evidence mounted of an association of the drugs with cancer — first in the 1970s with Premarin and endometrial cancer, then in the 1990s with Prempro and breast cancer — Wyeth tried to contain the concerns, the court documents show. (A note handwritten in 1996 by a Wyeth employee responding to a new report of breast cancer risks associated with hormone therapy said: "Dismiss/distract.")

In 2002, researchers halted the largest clinical trial ever conducted of women's health because participants who took certain combined hormones had an increased risk of breast cancer — as well as a higher risk of heart attack, stroke and blood clots in the lungs — compared with those taking a placebo.

Other parts of the same federal study, called the Women's Health Initiative, later found that hormone drugs increased the risk of dementia in a subset of participants, those age 65 and older.

Sales of Wyeth's hormone drugs peaked at about $2 billion in 2001, but after results of the 2002 study came out sales plummeted.

Pfizer is now fighting the Prempro litigation along with lawsuits over its progestin drug, Provera. Mr. Loder, the Pfizer spokesman, says Pfizer and Wyeth had fully informed patients, doctors and regulators of the risks of their menopause drugs, based on the best available science at the time of the disclosures.

"They provided accurate warnings, performed studies on benefits and risks, and kept the F.D.A. fully informed," he says.

But last month, a federal appellate court in St. Louis ruled in the case of a plaintiff named Donna Scroggin that Wyeth's inaction over accumulating evidence — and the company's attempts to mitigate cancer concerns by trying to undermine unfavorable scientific reports — could allow a jury to find Wyeth guilty of malicious conduct and award punitive damages.

For its part, Pfizer contends that two state judges in Pennsylvania have reached the opposite conclusion: that juries should not be allowed to award punitive damages because there was insufficient evidence of corporate misconduct.

Whichever direction the different cases ultimately follow, the court papers associated with them illustrate a pattern in the history of hormone therapy. First, many doctors enthusiastically prescribe hormone therapy drugs. Then a few researchers publish studies cautioning about risks, causing sales to fall. And finally, some doctors start prescribing a new iteration of hormone drugs.

For example, Prempro now comes in lower doses. Prempro labels say the drug should be prescribed for the shortest duration appropriate for the treatment goals and risks of the individual woman; previous labels on Wyeth's hormone drugs for decades gave the same advice. The current label also says that using estrogens, with or without progestins, may increase a woman's chance of heart attack, stroke, breast cancer and blood clots.

MENOPAUSAL hormone therapy has long been pitched as a way to stave off what some doctors viewed as the undesirable aspects of female aging.

In the popular 1966 book "Feminine Forever," Dr. Robert A. Wilson, a gynecologist, used disparaging descriptions of aging women ("flabby," "shrunken," "dull-minded," "desexed") to upend the prevailing idea of menopause as a normal stage of life. Women and their physicians, Dr. Wilson wrote, should regard menopause as a degenerative disease that could be prevented or cured with the use of hormone drugs.

"No woman can be sure of escaping the horror of this living decay," Dr. Wilson wrote. "There is no need for either valor or pretense. The need is for hormones."

Premarin had been available for decades, but Dr. Wilson's book propelled the idea of hormone "replacement" into the popular consciousness and onto physicians' prescription pads. The revivifying drugs promised to inhibit the ravages of time on the appearance and the psyche, Dr. Wilson wrote.

As the popularity of estrogen grew, an increasing number of women developed cancer of the uterine lining, the endometrium. In 1975, an F.D.A. panel concluded there was a link between Premarin and endometrial cancer. The company then sent a letter to doctors trying to mitigate such concerns, documents show.

"Dear Doctor," wrote Dr. John B. Jewell, at the time the medical director of Ayerst, the Wyeth predecessor. "It would be simplistic indeed to attribute an apparent increase in the diagnosis of endometrial carcinoma solely to estrogen therapy." Women may still receive "proven benefits," he wrote, by using "the lowest maintenance dose needed to control the menopausal symptoms." He added that the company planned to study the issue further.

F.D.A. officials then met with company officials, saying they were "incensed" that the letter was "intended to obfuscate the issues," according to a 1976 memo signed by the F.D.A. and the company. The F.D.A. said it would issue a bulletin saying there was a clear link between estrogen therapy and endometrial cancer. In 1976, the maker of Premarin added a warning to the label about the risk of endometrial cancer.

But the company never conducted further studies on the risk of developing endometrial cancer, according to the St. Louis appeals court decision.

The company instead focused its risk research on the possibility of breast cancers associated with hormone replacement therapy. But two studies published in the mid-1970s in The New England Journal of Medicine reported that taking estrogen therapy had increased the risk of endometrial cancer by at least five times.

Reports in 1975 about endometrial cancer "resulted in a precipitous decrease in estrogen use," according to a history of hormone therapy in The American Journal of Medicine in 2005.

In 1980, researchers at Boston University Medical Center estimated that the use of hormone therapy had caused more than 15,000 cases of endometrial cancer in the United States between 1971 and 1975 alone.

"This represents one of the largest epidemics of serious iatrogenic disease" — meaning disease caused by physician-administered treatments — "that has ever occurred in this country," the authors wrote. (Mr. Loder said Pfizer was not familiar with that report.)

Today, physicians prescribe Premarin to women who have had hysterectomies and therefore are not at risk for endometrial cancer.

BY the mid-1990s, after a few studies had reported a protective effect of hormone drugs on the heart, Wyeth had begun to reposition menopausal hormone therapy as a preventive health choice that could help inhibit heart disease and other maladies, according to court documents.

That marketing strategy coincided with the introduction of Wyeth's new combination hormone drug Prempro, which included a progestin hormone to keep estrogen from causing excessive cell growth in the uterine lining.

In one commercial from a Wyeth research institute, the model Lauren Hutton runs down a beach and warns of the health risks of estrogen loss.

"My doctor said if you don't replace estrogen that you lose at menopause, your risk for certain age-related diseases could increase," Ms. Hutton said in the commercial. In a voice-over, a narrator told viewers about studies looking into the connections between menopause and heart disease, memory loss and sight loss.

"Believe me," Ms. Hutton said, "the time to protect your future is now."

Sally Beatty, a spokeswoman for Pfizer, said this was a "help seeking" ad, of the type encouraged by the F.D.A. She added that the promotion did not mention any specific drugs, not did it suggest that drugs could cure the ailments described.

The labels for Premarin and Prempro at the time said the drugs were approved to treat moderate to severe symptoms of menopause like hot flashes, night sweats and vaginal dryness and to prevent

osteoporosis.

But Wyeth also positioned its menopausal hormone drugs as having larger protective benefits, court documents show.

Wyeth used proxies to promote a wide range of health benefits from hormone therapy, paying millions of dollars to influential doctors and medical groups and helping them develop abstracts for medical conferences and articles for medical journals, according to court documents.

The company also paid $12 million to sponsor continuing medical education programs from 2002 through 2006 at the University of Wisconsin, Madison. The programs, including an assertion that the Women's Health Initiative and another heart-risk study "miss the mark on quality of life," reached thousands of doctors.

Doctors were aware in the 1990s that hormone therapy could increase a woman's risk of breast cancer, says Dr. Carol Bates, the director of the primary care program at Beth Israel Deaconess Medical Center in Boston.

But based on the results of observational studies that had been published, many physicians, herself included, believed that the drugs' ostensible ability to reduce heart attacks and perhaps Alzheimer's would outweigh a breast cancer risk, she says.

"In the 1990s, there was actually tremendous pressure to put women on hormone therapy, and it came from a good place," Dr. Bates says. "But it was taken a bit to the extreme."

HORMONE therapy — aimed at the symptoms it effectively treats and with full disclosure about its possible risks — has many advocates. Dr. Lynne T. Shuster, the director of the women's health clinic at the Mayo Clinic in Rochester, Minn., says such regimens can be very worthwhile for treating hot flashes, night sweats and vaginal dryness associated with menopause.

And some users agree.

Irene Fisher, a kitchen and bath designer in Baldwin, N.Y., says she has been taking Prempro for 16 years to control hot flashes and night sweats.

"I always feel good when I take it," she says. The benefits are worth a small risk, Ms. Fisher says, adding that she has an annual mammogram to check for breast cancer and that "I think you have to know your own body."

But many women were not so fully informed in the 1990s.

In 1996, for example, a federal study reported that breast cancer risk may have been "substantially underestimated." Wyeth reacted with plans to dismiss it as "just one more paper," and try to "overshadow" it by directing journalists to other studies, according to documents cited in the court

of appeals decision in Missouri.

In 1997, Wyeth began working with DesignWrite, a company in Princeton, N.J., that is paid by drug makers to develop manuscripts for publication in medical journals. The specific objective of a publication plan for Premarin was to "increase physician awareness on the multitude of benefits that hormone replacement therapy provides" and "diminish the negative perceptions associated with estrogens and cancer," according to a 1997 DesignWrite proposal prepared for Wyeth.

Over the next decade, Wyeth paid DesignWrite to prepare at least 60 articles for publication in medical journals on the potential benefits of hormone therapy for cardiovascular disease, Alzheimer's disease, diabetes, colon cancer, vision loss and other health problems, the court documents show.

In response to an e-mail query, Michael Platt, president of DesignWrite, wrote that the articles were all medically and scientifically accurate and valid and peer reviewed.

But Wyeth's and DesignWrite's effort hit an obstacle in 2002 when researchers reported the results of the Women's Health Initiative.

The National Institutes of Health ultimately decided to start using the term "menopausal hormone therapy" instead of "hormone replacement therapy," says Marcia L. Stefanick, a professor of medicine at the Stanford University medical school who was principal investigator on the Women's Health Initiative study at her institution.

While the drugs are effective at treating symptoms like hot flashes, she says, the word "replacement" implies that women need hormone drugs after menopause. "But there is no good evidence that women need this after menopause," Professor Stefanick says.

In 2003, Wyeth added a "black box" warning to the label saying Prempro should not be prescribed to prevent cardiovascular disease.

The same year, the F.D.A. approved a lower dose version of Prempro so women would have more options.

Today, many doctors who once offered hormone therapy to women without symptoms like hot flashes limit the use of the drug to those with symptoms, prescribing low doses for a short time.

"Right now, the big difference is we do not recommend hormone therapy for good health or health promotion or anti-aging," says Dr. Shuster of the Mayo Clinic.

And even with lower-dose hormones, doctors do not have a uniform view on what constitutes the optimal duration.

Dr. Adriane Fugh-Berman, an associate professor at the medical school of Georgetown University,

considers both Premarin and Prempro examples of drugs that gained widespread popularity before science had established the full extent of their risks.

“Where there has always been a push is where there isn’t data,” says Dr. Fugh-Berman, who has been a paid expert witness for plaintiffs in the hormone litigation. “Now, low-dose hormones are being pushed.”

LIKE Dr. Wilson, the gynecologist in the 1960s who identified the evils of menopause, contemporary voices are advocating hormones as an anti-aging treatment.

The actress Suzanne Somers, for example, has identified her own lineup of maladies, which she calls the Seven Dwarves of Menopause: “Itchy. Bitchy. Sweaty. Sleepy. Bloated. Forgetful. All Dried Up.”

In books with titles like “The Sexy Years” and “Ageless,” Ms. Somers has promoted the use of “bio-identical” hormones, which can be prescribed by doctors in customized doses and can be prepared individually by pharmacies.

But Dr. Shuster of the Mayo Clinic says the hormones have not been extensively studied for safety and efficacy. And, unlike branded hormone therapy, she says, they have not been approved by the F.D.A.

Women, Dr. Shuster says, should not assume that compounded hormones are safer than F.D.A.-approved menopausal hormone drugs. Nevertheless, with sales of more than two million books, Ms. Somers has become a menopause guru to millions.

“I think I had a lot to do with making the word ‘menopause’ mentionable,” Ms. Somers, 63, said in a phone interview last week. She said the compounded hormones were safe, and she sent some articles from medical journals to back up her point.

In fact, much of Ms. Somers’s description of menopause as a deficiency that can be rebalanced with hormones sounds like a modern take on “Feminine Forever.”

“Hormones,” Ms. Somers said last week, “are the juice of life.”