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Wyeth Pharmaceuticals

Premarin®, Prempro® and Hormone Replacement Therapy

> "These results [from the Women's Health Initiative] are valuable new data with significant implications. However, it is also important to recognize the critical role that combination Hormone Replacement Therapy (HRT) plays in treating the symptoms of menopause is the *number one* reason that women start therapy. In a recent survey, doctors report that management of symptoms is a treatment goal for nine out of ten new patients starts with combination HRT."

Victoria Kusiak, M.D.,V.P., Clinical Affairs and North American Medical Director, July 2002

On a hot, humid morning in early July in Madison, New Jersey, Justin Victoria, Vice President of Investor Relations at Wyeth, listens intently to a conference call. In Philadelphia, Pennsylvania, Natalie de Vane, Vice President of Corporate Communications, and her team just dialed into the same call. Executives at Wyeth Pharmaceutical recently returned from an "emergency meeting" with researchers at the National Heart, Lung, and Blood Institute (NHLBI), a division of the National Institutes of Health (NIH). The NHLBI in conjunction with other divisions of the NIH was conducting a study regarding the risks and benefits associated with the long-term use of HRT. Wyeth had supplied the HRT used during the WHI trials – Premarin® was used in the estrogen alone trial, and Prempro® was used in the estrogen-plus-progestin trial.

The information they were sharing caught everyone by surprise. During the conference call, Wyeth executives conveyed that the Data and Safety Monitoring Board (DSMB) of the Women's Health Initiative (WHI) study had decided to discontinue the estrogen-plus-progestin, or combination HRT arm of the study, citing increased risks of cardiovascular disease and, over time, an increased risk of breast cancer. The NIH claimed there were noteworthy benefits of
using Prempro in the long-term, including fewer cases of hip fractures and colon cancer. The clinical trial for the

combination HRT arm of the study was terminated over a month ago. The

This case was prepared by Research Assistants Kathryn I. C. Huang and Megan E. Vanaelstyn under the direction of James S. O'Rourke, Concurrent Professor of Management, as the basis for class discussion rather than to illustrate either effective or ineffective handling of an administrative situation.

long-term benefits of hormone replacement therapy, including the prevention of heart disease did not turn up as expected.

The executives continued with their disheartening news by stating that *The Journal of the American Medical Association (JAMA)* would be releasing the results of the study in its July issue, which would be available to the medical community the following week. In response, Wyeth immediately alerted physicians by sending out 550,000 letters informing them of the study and the facts of the findings. The letter also included a copy of the article that was to appear in *JAMA.* In anticipation of queries by patients and physicians, Natalie de Vane and her team established separate toll-free numbers for physicians who prescribe the medication and for patients who use the medication.

History of Wyeth Laboratories

Wyeth began as a small drug store called "John Wyeth & Brother." It was founded by John Wyeth and his brother in 1860 in Philadelphia, Pennsylvania. In 1931, American Home Products Corporation (AHP) purchased Wyeth and started acquiring other pharmaceutical companies including, Ayerst, McKenna & Harrision, and Lederle Laboratories. In March 2002, after being known as AHP for 76 years, AHP changed its name and trading symbol to Wyeth (NYSE:WYE). For the past decade, Wyeth has seen steady increases in its share price. In recent years, its stock has been trading around $60 per share. With over 52,000 employees, Wyeth is comprised of four divisions: Wyeth Pharmaceuticals, Wyeth Research, Wyeth Consumer Healthcare, and Fort Dodge Animal Health.[1]

Wyeth Pharmaceuticals manufactures and markets several well-known brands including Premarin®, Advil, Effexor, and Centrum. Wyeth's portfolio of popular women's health drugs – the Premarin® family of products -- is aimed at preventing symptoms of menopause and is Wyeth's largest and most successful group of

[1] http://www.wyeth.com.

treatments[2]. In 2001, more than 11 million women used a Premarin® product for menopausal symptoms and osteoporosis.[3]

The Premarin® family of products, which includes Premarin®, a blend of natural estrogens (for women who have had a hysterectomy); Prempro®, a one-tablet hormone replacement therapy consisting of natural estrogens plus progestin (for post-menopausal women with an intact uterus); and Premphase®, a blend of natural estrogens plus progestin (given 14-days out of the cycle) generated sales of over $2 billion in 2001 and accounted for 14% of total net revenues.[4]

Menopause

For most women, the most basic and personal definition of menopause is the cessation of menstruation. Underlying that change on a basic biological level is the disappearance of a woman's eggs from her ovaries. That loss does not occur abruptly, but over the decades of a woman's life leading up to menopause. A baby girl comes into the world with about 2 million immature eggs. By age 12, the count is already down to 300,000 eggs, and by the time a woman reaches her late 30's, the count is down to 25,000. A woman experiences barely 400 menstrual cycles in her life, yet finds her ovaries eggless by middle age.[5] No one in the scientific or medical community truly understands this phenomenon.

The Unspoken Effects of Menopause

Menopause can be extremely bothersome for some patients, and debilitating for others.[6] Menopause causes a woman's body to slow down the production of estrogen, which is a natural hormone, produced by the ovaries. By the time natural menopause is complete – usually between the ages 45 and 55 – hormone output has decreased significantly. The reduction in the amount of estrogen in a woman's body can have wide-ranging effects – from symptoms such as hot flashes, night sweats, fatigue, irritability and mood changes, to underlying effects like an increased risk of osteoporosis.[7]

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[2] "Wyeth Puts Health Warning on Hormone Replacement," *New York Times,* September 5, 2002.
[3] Wyeth, Annual Report 2000.
[4] http://www.premarin.com/womans_hormones.html
[5] Healy, Dr. Bernadine, "The Mysteries of Menopause," *US News & World Report*, November 18, 2002.
[6] Abeloff: Clinical Oncology, 2nd ed., copyright 2000 Churchill Livingstone, Inc.
[7] http://www.premarin.com/vaginal_symptoms.html.

The most dramatic side effect is the hot flash, a clear signal that estrogen receptors of the brain are in uproar. Typically, as the first hot flash occurs, calcium pours out of the bones and bone cells begin degenerating tissue at a faster pace than the tissue is replaced. The cardiovascular system loses its protection from hardening of the arteries that had been offered by pre-menopausal ovaries. Varying in intensity and lasting for seconds to minutes, a sudden flush makes a woman feel overwhelmingly hot, sometimes with drenching perspiration, palpitations, and even a wave of anxiety, followed by a shiver. Soaked clothes and bed sheets can be annoying and embarrassing. Hot flashes usually subside over time and most are gone within a year or two.[8]

What is Hormone Replacement Therapy?

For years, doctors have recommended HRT as a method to help women manage the symptoms of menopause, as well as to help postmenopausal women maintain a healthy hormone level. Since estrogen loss is thought to put more women at risk for more serious health problems, doctors were quick to prescribe HRT. Taking HRT for a short time (perhaps a few years) is thought to help women relieve the annoying symptoms associated with menopause. Taking hormone supplements for a longer time was thought to help against such serious problems as stroke, osteoporosis, as well as the leading cause of death for women over the age of 50: heart disease.

The Controversy of HRT

The HRT area remains controversial with clinical results often painting a contradictive and confusing picture on the relative safety profile of drugs such as Premarin® and Prempro®. Despite decades of accumulated evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain.

The NIH's recent findings are not the first study to suggest that a woman's risk of breast cancer rises the longer she is on HRT. In 1997, researchers reported a substantial increase in the risk of breast cancer among women, particularly older women on HRT, and noted that the addition of progesterone, which was commonly thought to decrease the risk of breast cancer, actually

[8] Healy, Dr. Bernadine, "The Mysteries of Menopause," US News & World Report, November 18, 2002.

failed to reduce any risk.[9] Exhibit I details the trials and tribulations of HRT in the United States.

The Medical Disconnect

The first estrogen, estrone, was synthesized in Germany in 1928. In 1959, two doctors argued that simply replacing the body's lost estrogen could reverse all the negative symptoms associated with menopause. Estrogen sales soared. In 1975, prevalent medical opinion was thrown into a tailspin when the *New England Journal of Medicine* published two studies showing that women who took estrogen had four or more times as great a risk of developing endometrial cancer as those who did not. Among women who took the hormone longer, the cancer risk increased. As a result, estrogen sales plummeted.[10]

To combat the declining sales, in 1985 Wyeth conducted an aggressive media relations campaign to create public awareness of osteoporosis, a bone loss disease that affects 25% of post-menopausal women and leads to high risk of fractures. Osteoporosis was a deadly disease for which HRT was one possible remedy. Wyeth urged women to consult with their doctors.[11] In addition to providing prevention for Osteoporosis, researchers realized if hormones were demonstrated to protect the cardiovascular system, then HRT could be promoted as a necessary treatment for heart disease.

Initial results regarding HRT's effect on heart disease were somewhat unclear, as there appeared to be inconsistencies with the long-term benefits of using HRT. That soon changed when researchers began releasing positive studies supporting hormones in preventing heart attacks, and bone loss, while not increasing cancer, stroke, or blood clots.[12] Based on these observational studies, Wyeth asked the FDA to approve a label change to include heart disease prevention in women without a uterus. In June 1990, Wyeth was granted the label change. Notably, the standard *Physicians' Desk Reference* at that time suggested that estrogen should not be prescribed to women with heart disease, hypertension, or diabetes.

That same year, the NIH launched a significantly large clinical trial on women's health – which would later be globally recognized as The Women's Health Initiative – covering heart

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[9] http://www.health.discovery.com/centers/womens/hrt/controversy_print.html.
[10] Spake, Amanda, "The Menopausal Marketplace," *US News & World Report*, November 18, 2002.
[11] Spake, Amanda, "The Menopausal Marketplace," *US News & World Report*, November 18, 2002.
[12] Spake, Amanda, "The Menopausal Marketplace," *US News & World Report*, November 18, 2002.

disease, breast and colon cancer, bone fractures, and the roles of hormone therapy, diet, vitamins and calcium in preventing these diseases. Women, doctors, and even researchers were confused and increasingly concerned about the long-term use of HRT and the risks associated with various forms of cancer.[13]

Prempro®

Estrogen was the dominant hormone used in HRT until the increased risk of endometrial cancer led to the addition of progestin for women with an intact uterus. Since the mid 1980s, combined estrogen/progestin use has steadily increased. Progestin is a synthetic form of the natural hormone progesterone. In 1995, Wyeth began marketing Prempro® as the first estrogen-plus-progestin HRT pill approved by the FDA. In addition to countering the negative side effects of menopause, Prempro® reduces the risks of colon cancer and hip fracture by about one-third. That same year, Wyeth's Prempro® sales soared to US$22 million.

In 2001, approximately 22.3 million prescriptions were written for Prempro®. Domestic sales increased by 9.29% from US$686.3 million in 2000 to US$749.7 million in 2001. However, after the WHI study was made public, Credit Swiss First Boston analysts were estimating that sales for Prempro® would decrease by -13.4%, -38.1%, and -15.8% in 2002, 2003, and 2004, respectively.[14]

Analysts at Dredsner Kleinwort Wasserstein report that prescriptions for both Premarin® and Prempro® have been negatively impacted by the WHI study as shown in Exhibit II.

National Institutes of Health

The National Institutes of Health or NIH is one of the agencies of the Public Health Services that is part of the U.S Department of Health and Human Services. Comprised of 27 separate components, mainly Institutes and Centers, NIH occupies more than 75 buildings on more than 300 acres in Bethesda, Maryland. The goal of all NIH research is to acquire new knowledge to help prevent, detect, diagnose, and treat disease

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[13] Spake, Amanda, "The Menopausal Marketplace," *US News & World Report*, November 18, 2002.
[14] Credit Swiss First Boston, July 7, 2002.

and disability, from the rarest genetic disorder to the common cold.[15]

Women's Health Initiative

The Women's Health Initiative (WHI), sponsored by NIH, is a 15-year study focusing on the prevention of heart disease, breast and colorectal cancer, and osteoporosis. The study was scheduled to conclude in 2005. WHI, which consists of a set of clinical studies and an observational study, began in 1991 and involved healthy postmenopausal women. Two specific drugs were used during the study, Premarin® and Prempro®, both supplied by Wyeth.

On May 31, 2002, the DSMB, charged with reviewing the results of the clinical trials and ensuring participant safety, recommended that the trials of the estrogen plus progestin arm of the study be stopped. WHI decided to discontinue the Prempro arm of the study, citing an increased risk of invasive breast cancer as the main factor. The NIH stated that there is currently no evidence of increased risk of breast cancer in women taking estrogen alone (Premarin®) in the trial. Therefore, that part of the trial will continue until 2005.

Specifically, the Prempro® arm of the clinical study involved 16,608 healthy women who either took estrogen-plus-progestin or a placebo. The women were between the ages of 50 and 70 and still had a uterus. The main goal was to see if the therapy would help prevent heart disease and hip fractures. Another goal was to see if these potential benefits were greater than the possible risks for breast cancer, endometrial cancer and blood clots. The goal of the study was not to determine if HRT was effective in treating the symptoms associated with menopause. The study, which was scheduled to run for 8.5 years, was stopped early. After 5.2 years, researchers felt the therapy's risks overshadowed the benefits.

The study results showed that combination HRT therapy resulted in a 26% increase in breast cancer. While no deaths from breast cancer occurred as a direct result of the combined therapy, this factor alone was reason enough to immediately halt the study. The Estrogen-plus-progestin therapy compared to the placebo group also resulted in:

1. 41% increase in strokes
2. 29% increase in heart attacks
3. Doubled rates of blood clots in legs and lungs[16]

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[15] http://www.nih.gov/
[16] http://www.nhlbi.nih.gov/whi/

4. 37% reduction in colorectal cancer
5. 34% reduction in hip fractures

Stated differently, after an average of 5.2 years, the study indicate that if 10,000 postmenopausal women were taking estrogen and progestin, 8 more will have invasive breast cancer versus the placebo group – 38 women versus 30 women, which reflects a 26% increase. Seven more women will have a heart attack - 37 women versus 30 women, which reflects a 29% increase. Eight more women will have a stroke – 29 women versus 21 women, which reflects a 41% increase. Eighteen more women will have blood clots compared to those women who are not taking combination HRT.[17]

On the other hand, the study indicates that women taking estrogen-plus-progestin saw a reduction of colorectal cancer by 37% - 10 women versus 16 women taking a placebo, and a reduction of hip fractures by 35% - 10 versus 15 women taking a placebo. See Exhibit III for the relative and absolute risk benefits of the study as adapted from the WHI findings.

Physicians Put the Risks of HRT in Perspective

While middle-aged women across the country began panicking as they tried to understand what this study meant to them personally, doctors around the country began admitting that perhaps they had been too quick to prescribe hormone replacement therapy for symptoms common in middle-aged women.

"This study hasn't changed my practice. We've known of breast cancer risk associated with HRT for some time, and we've known that women with heart disease didn't get much benefit from HRT," said Steven Goldstein, professor of obstetrics and gynecology at NYU School of Medicine. "This study never addressed the women who come to menopause with terrible symptoms. Women should still take HRT in the short term, but on a case-by-case basis. Patients are individuals and should be treated one at a time."

"For women who suffer with heart palpitations, mood swings, night sweats or dryness of tissues, HRT can be a Godsend," said Cardiologist Stephen Sinatra, founder of the New England Heart and Longevity Center in Manchester, Connecticut. "If a woman takes HRT, it must be for quality of life issues. It's important to realize that the stress from these symptoms alone can precipitate coronary disease. It really is a double-edge sword."[18]

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[17] http://www.hrt-debate.com/html/new_information.php3
[18] http://www.health.discovery.com/centers/womens/hrt/controversy_print.html

"The NIH study in question showed a slight increase for the risk of cancer and heart disease in less than one tenth of one percent of the women studied," responded Dr. Judith Reichman, author of *Relax, This Won't Hurt.* "We thought that estrogen was going to help protect our hearts. What we found out was that Prempro® does not; there are questions if estrogen, in general, will. But the thought of just giving everyone hormones and saying, 'Here, dear, take this forever and this will prevent all diseases,' we now realize is not true."[19]

The Problem Escalates

On July 9, 2002 at 9:30 a.m. Eastern Time, the NIH formally releases its findings to the public in a press release.[20] At nearly the same time, Wyeth issues a press release to "Inform Physicians of the WHI findings."[21]

Within hours, the national online media outlets pick up the story. Gynecologists' offices across the United States are swarmed with calls as their patients try to understand how soon they should stop taking HRT. By the next morning, headlines were screaming from coast to coast and across the world sending millions of women into a panic.

"Halted HRT study raises questions" (*USA Today,* July 10, 2002).[22]

"Hormone Therapy Harm Found Risks for Women Seen in Long Term" (*The Boston Globe,* July 10, 2002).[23]

"Wyeth Stock Falls 24% after Report" (*The New York Times,* July 10, 2002).[24]

"Dangers of Popular Prempro Worry Doctors and Patients" (*The Houston Chronicle,* July 10, 2002).[25]

"HRT Trial Cancelled Over Cancer and Stroke Fears" (*The Guardian,* July 10, 2002).[26]

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[19] http://www.oprah.com/tows/pastshows/tows_2002/tows_past_20021010_d.jhtml.
[20] http://www.wyeth.com/news/Pressed_and_Released/pr07_09_2002.asp.
[21] http://www.nhlbi.nih.gov/new/press/02-07-09.htm.
[22] "Halted HRT Study Raises Questions,"*USAToday,* July 10, 2002.
[23] "Hormone Therapy Harm Found Risks for Women Seen in Long Term," *The Boston Globe,* July 10, 2002.
[24] "Wyeth Stock Falls 24% after Report," *The New York Times,* July 10, 2002.
[25] Dangers of Popular Prempro™ Worry Doctors and Patients" *The Houston Chronicle,* July 10, 2002,

Late that afternoon, the Philadelphia based law firm Schiffrin & Barroway, specializing in consumer class action litigation, commenced an investigation into possible legal actions against Wyeth.[27]

Not Just Another Day at Work

After another exhausting conference call, Justin and Natalie returned to their offices to find the media inundated with writing HRT stories, many of which are not accurately reflecting the true findings of the study. Justin focuses his attention on the share price and hopes that the market will not further punish the company on the conclusions of the WHI study. As shown in Exhibit IV, share prices of WYE dropped to US$38 dollars per share since the release of the *JAMA* article the previous day.

Natalie de Vane and her team know they need to communicate immediately that the NIH study *did not* evaluate the use of combination HRT for the treatment of menopausal symptoms or vaginal atrophy, the foremost reason HRT is prescribed. Additionally, the team knows they need to emphasize the important fact that an increase in the relative risk of breast cancer did not occur until the patient had been on the drug for longer than four years.

Questions

1. How should Wyeth Pharmaceuticals respond to the findings of the NIH study?

2. What are the issues for Natalie de Vane and the corporate communications team to address at this point?

3. Who are the key audiences that Wyeth should try to reach and through what means?

4. Who are the relevant stakeholders?

5. Over the years, numerous scientific and medical sources have reached different conclusions on HRT. Armed with the new WHI data, how should Wyeth move forward?

6. If, in fact, HRT poses a greater threat than benefit to women in the long term, is it ethical for the company to continue the marketing of this product? What are the corporate ethical issues involved when a pharmaceutical company

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[26] "HRT Trial Cancelled Over Cancer and Stroke Fears," *The Guardian,* July 10, 2002.

[27] http://www.classactionamerica.com/cases/case.asp?cid=1710.

attempts to market its products into market segments that have not been scientifically or medically founded?

Exhibit I: The Trials and Tribulations of HRT

1942 Wyeth's Premarin®, the nation's first hormone replacement drug, hits the market.

1959 Study shows that estrogen protects bones and relieves menopausal symptoms.

1962 Medical expert Robert Wilson claims that estrogen during menopause reduces breast and genital cancers.

1966 FDA says that Wilson's recommendations go beyond approved data and that it will no longer support his data.

1973 *Harper's Bazaar* declares: "There doesn't seem to be a sexy thing that 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."

1975 More than 30 million prescriptions for estrogen are written every year. Half of all menopausal women are using HRT for a median of five years.

Two studies published in the *New England Journal of Medicine* show that post-menopausal estrogen use increases endometrial cancer risk four to 14 times.

Wyeth's Premarin® is the fifth most frequently prescribed drug.

1976 *The New England Journal of Medicine* publishes the first study showing a link between menopausal estrogen and breast cancer.

1980 The Journal of *Obstetrics and Gynecology* reports that adding progestin to estrogen led to a decline in endometrial cancer.

1982 Medical experts claim that estrogen-progestin combination may help osteoporosis and may "have protective effects against cardiovascular disease." At the same time, experts claim that menopausal hormones are a major factor in cancer in the medical periodical *Cancer Research.*

1989 *The New England Journal of Medicine* releases findings that show a slight increase in breast cancer among those who took estrogen. When women switched to combination HRT, their breast cancer risk more than doubled.

1990/95 Wyeth's Premarin® is the most frequently prescribed prescription drug in the U.S.

1995 Wyeth's Prempro®, the first estrogen-plus-progestin HRT pill, is approved by the FDA.

2000 The Women's Health Initiative tells study participants that some women are experiencing heart attacks and strokes and offers them the opportunity to drop out.

2002 The Women's Health Initiative com

Exhibit II – Prescriptions for Wyeth HRT

Total Weekly Rx for Wyeth HRT				
Week	**Premarin**	**Premphase**	**Prempro**	**Total**
5-Jul	729,910	33,685	352,212	1,115,807
12-Jul	731,572	31,909	331,219	1,094,700
19-Jul	661,839	27,479	271,410	960,728
26-Jul	626,384	27,858	248,727	902,969
2-Aug	679,904	28,915	253,948	962,767
Q4 01 Avg:	785,434	37,694	387,083	1,210,211
Q1 02 Avg:	776,916	37,128	384,424	1,198,468
Q2 02 Avg:	762,233	35,801	376,522	1,174,556
Q3 02 Avg:	685,922	29,969	291,503	1,007,394

Total New Rx for Wyeth HRT				
Week	**Premarin**	**Premphase**	**Prempro**	**Total**
5-Jul	183,056	7,902	82,313	273,271
12-Jul	194,095	7,545	78,056	279,696
19-Jul	175,191	6,203	59,943	241,337
26-Jul	166,748	6,018	52,137	224,903
2-Aug	176,091	6,306	52,282	234,679
Q4 01 Avg:	233,586	9,275	95,558	338,419
Q1 02 Avg:	227,110	9,343	98,753	335,206
Q2 02 Avg:	206,323	9,134	92,155	307,612
Q3 02 Avg:	179,036	6,795	64,948	250,779

Source: Dredsner Kleinwort Wasserstein, *Hormone Replacement Therapy*, August 12, 2002
See Exhibit III for the relative and absolute risk benefits of the study as adapted from the WHI findings.

[28]Spake, Amanda, "The Menopausal Marketplace," *US News & World Report*, November 18, 2002.

Exhibit III: The Relative and Absolute Risks / Benefits from HRT from WHI Study

Health Event	Relative Risk vs. Placebo Group at 5.2 Years	Increased Absolute Risk per 10,000 Women/Year	Increased Absolute Benefit per 10,000 Women/Year
Heart Attacks	1.29	7	
Strokes	1.41	8	
Breast Cancer	1.26	8	
Blood Clots	2.11	18	
Colorectal Cancer	0.63		6
Hip Fractures	0.66		5

Source: Wyeth Pharmaceuticals, Press Release, July 2002

Exhibit IV – Share Price Effect


Wyeth
as of 11-Nov-2002
Splits:
70
60
50
40
30
20
Jan02
Mar02
May02
Jul02
Sep02
60
40
20
0
Millions
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