

Women's Health

Companies in this space are expanding beyond reproductive health into areas like menopause and osteoporosis, where safety concerns hamper existing drugs and patient need is being driven secondary to aging. To succeed, they'll need to re-energize their physician and patient base. **Noah Pines** reports

Pharmaceutical companies in the women's health space are redoubling efforts to expand beyond reproductive health into areas where existing therapies have been hampered by safety concerns—and where big patient need is being driven secondary to aging. The unmet need is not just for better, safer products. Manufacturers also must re-energize physicians and patients who have become disillusioned and, in many cases, have de-prioritized (and under-treated) these conditions.

Noven Therapeutics' Brisdelle is vying to fill the void. Approved in July, it's the first non-hormonal drug to address moderate-to-severe hot flashes and night sweats associated with menopause.

"About half of post-menopausal women experience vasomotor symptoms, including hot flashes," and of these, "nearly a third sees them as moderate-to-severe," says Dr. Marco DiBonaventura, VP of health outcomes, Kantar Health.

Brisdelle is essentially a lower-dose version of GlaxoSmithKline's Paxil (paroxetine), an anti-depressant that's been used off-label to

treat hot flashes for years. Brisdelle's launch is slated for November. Generic paroxetine may not be the only headwind it faces.

FDA approved the drug even though it lacked an endorsement by the agency's independent advisory committee, which did not see sufficient advantage over placebo in reducing severity and number of hot flashes—a reduction of fewer than two per day was seen in testing.

An agency official cited the unmet need as the deciding factor or, as he put it, a "significant number of women who suffer from hot flashes associated with menopause and who cannot or do not want to use hormonal treatments." The approval also sends a signal to industry, says *in*Thought analyst Dr. Michael Zuckerman, who says, "It opens the door to new products."

Over the next five to six years, new agents like Brisdelle, and other products, including vaginal atrophy drugs like Shionogi's recently approved Ospemifene, are expected to drive growth in the women's health field, whose total sales rose 3% last year to \$12.7 billion, according to figures from IMS Health.

Analysts anticipate the products will boost patient adherence through improved safety and efficacy profiles. Due to those hormone replacement therapy (HRT) safety concerns, companies will need to help primary care physicians and patients get reacquainted through disease-awareness campaigns to improve diagnosis and treatment-seeking behaviors. The renewed push comes a decade after results of the NIH's Women's Health Initiative (WHI) demonstrated that women taking HRT may be at increased risk of some invasive breast cancers and stroke.

"When I was a resident, the thinking was to give HRT to almost every woman as it was good not only for the symptoms of menopause but also for maintaining brain and heart health and decreasing the



TOP 50 WOMEN'S HEALTH PRODUCTS, 2012

Category leaders, ranked by US sales, and their media spend

Rank	Product	Manufacturer	US sales \$ (millions)*	Vs. prior 12 mos.	TRx (000s)	Vs. prior 12 mos.	US DTC media \$ (000s)	Vs. prior 12 mos.	US journal media \$ (000s)	Vs. prior 12 mos.
1	Evista	Eli Lilly	\$779.4	1.0%	3,336.0	-11.0%	\$81.3	-99.0%	\$1,512.0	-32.8%
2	Xgeva	Amgen	\$663.4	85.0%	5.0	100.0%	\$10.2	63.0%	\$2,346.0	-2.4%
3	Mirena	Bayer	\$654.8	43.0%	28.0	-23.0%	\$13,800.7	-43.0%	\$297.0	-44.2%
4	Zometa	Novartis	\$612.1	-9.0%	7.0	-17.0%	\$9.0	-65.0%	\$1,093.0	-28.8%
5	Loestrin 24 FE	Warner Chilcott	\$540.7	-6.0%	6,220.0	-16.0%	\$0.0	N/A	\$0.0	-100.0%
6	NuvaRing	Merck	\$517.0	5.0%	5,189.0	-3.0%	\$25,764.8	1.0%	\$34.0	-38.6%
7	Forteo	Eli Lilly	\$507.1	1.0%	405.0	-4.0%	\$0.0	N/A	\$2,413.0	-24.0%
8	Premarin	Pfizer	\$500.1	-1.0%	5,224.0	-15.0%	\$24,860.4	-25.0%	\$450.0	N/A
9	Actonel	Warner Chilcott	\$436.4	-28.0%	2,503.0	-36.0%	\$0.0	N/A	\$0.0	N/A
10	Ortho-Tri-Cy Lo 28	Janssen	\$432.9	-1.0%	3,594.0	-16.0%	\$0.0	-100.0%	\$0.0	N/A
11	Reclast	Novartis	\$362.4	-10.0%	13.0	-7.0%	\$17,056.3	-56.0%	\$0.0	-100.0%
12	Prolia	Amgen	\$304.3	>100.0%	109.0	>100.0%	\$60,212.4	>100.0%	\$2.0	-99.8%
13	Vivelle-Dot	Novartis	\$294.1	15.0%	3,502.0	5.0%	\$0.0	N/A	\$0.0	N/A
14	Premarin Vaginal	Pfizer	\$265.9	21.0%	1,624.0	0.0%	\$0.0	N/A	\$245.0	-65.9%
15	Follistim AQ	Merck	\$245.3	8.0%	113.0	-6.0%	\$0.0	N/A	\$0.0	N/A
16	Vagifem	Novo Nordisk	\$207.5	17.0%	1,963.0	-2.0%	\$0.0	-100.0%	\$103.0	-73.0%
17	Estrace	Warner Chilcott	\$205.4	17.0%	1,609.0	13.0%	\$0.0	N/A	\$0.0	N/A
18	Ibandronate sodium	Generic	\$189.1	N/A	1,496.0	N/A	\$0.0	N/A	\$0.0	N/A
19	Boniva	Genentech	\$173.0	-72.0%	847.0	-75.0%	\$10,404.3	-81.0%	\$0.0	N/A
20	Lo Loestrin FE	Warner Chilcott	\$163.1	>100.0%	2,068.0	>100.0%	\$0.0	-100.0%	\$0.0	N/A
21	Prempro Low Dose	Pfizer	\$160.3	4.0%	1,417.0	-10.0%	\$0.0	N/A	\$0.0	-100.0%
22	Gianvi	Teva	\$146.8	-49.0%	2,708.0	-40.0%	\$0.0	N/A	\$0.0	N/A
23	Medroxyprogesteron	Generic	\$146.1	22.0%	4,218.0	3.0%	\$0.0	N/A	\$0.0	N/A
24	Ortho Evra 3	Janssen	\$138.5	3.0%	1,238.0	-10.0%	\$0.0	N/A	\$0.0	N/A
25	Progesterone	Generic	\$131.4	N/A	1,684.0	>100.0%	\$0.0	N/A	\$56.0	N/A
26	Beyaz-28	Bayer	\$128.9	32.0%	1,544.0	25.0%	\$0.0	-100.0%	\$0.0	-100.0%
27	Loryna	Sandoz	\$119.2	69.0%	1,288.0	115.0%	\$0.0	N/A	\$0.0	N/A
28	Ocella	Teva	\$110.1	-28.0%	1,856.0	-25.0%	\$0.0	N/A	\$0.0	N/A
29	Tri-Sprintec-28	Teva	\$101.5	-18.0%	4,308.0	-9.0%	\$0.0	N/A	\$0.0	N/A
30	Gonal-F RFF	EMD Serono	\$97.8	17.0%	29.0	14.0%	\$0.0	N/A	\$0.0	N/A
31	Camrese	Teva	\$93.2	>100.0%	478.0	>100.0%	\$0.0	N/A	\$0.0	N/A
32	Prempro	Pfizer	\$83.9	4.0%	811.0	-11.0%	\$0.0	N/A	\$0.0	N/A
33	Plan B One-Step	Teva	\$82.8	-11.0%	108.0	-26.0%	\$15,199.2	20.0%	\$0.0	N/A
34	Yaz-28	Bayer	\$76.0	-49.0%	794.0	-56.0%	\$0.0	N/A	\$0.0	-100.0%
35	Atelvia	Warner Chilcott	\$74.6	99.0%	522.0	81.0%	\$0.0	-100.0%	\$0.0	-100.0%
36	Norgest/Eth Estr	Generic	\$68.4	>100.0%	1,892.0	>100.0%	\$0.0	N/A	\$0.0	N/A
37	Zarah	Actavis	\$62.9	-32.0%	1,086.0	-36.0%	\$0.0	N/A	\$0.0	N/A
38	Estradiol/Noreth A	Generic	\$61.2	83.0%	818.0	47.0%	\$0.0	N/A	\$0.0	N/A
39	Prometrium	AbbVie	\$61.0	-70.0%	711.0	-69.0%	\$0.0	-100.0%	\$0.0	-100.0%
40	Sprintec 28	Teva	\$57.0	29.0%	3,692.0	31.0%	\$0.0	N/A	\$0.0	N/A
41	Estring	Pfizer	\$56.9	2.0%	312.0	2.0%	\$13,985.8	100.0%	\$0.0	N/A
42	Next Choice	Actavis	\$56.4	-31.0%	153.0	-34.0%	\$0.0	N/A	\$0.0	N/A
43	Estradiol Transdml	Generic	\$55.7	22.0%	924.0	7.0%	\$0.0	N/A	\$0.0	N/A
44	Menopur	Ferring	\$55.6	11.0%	75.0	12.0%	\$0.0	N/A	\$117.0	>100.0%
45	Premarin Low Dose	Pfizer	\$54.8	-2.0%	531.0	-15.0%	\$0.0	N/A	\$450.0	N/A
46	Syeda	Sandoz	\$53.9	>100.0%	550.0	>100.0%	\$0.0	N/A	\$0.0	N/A
47	Trinessa-28	Actavis	\$53.0	-18.0%	4,431.0	-8.0%	\$0.0	N/A	\$0.0	N/A
48	Alendronate sodium	Generic	\$47.7	-21.0%	13,346.0	-15.0%	\$0.0	N/A	\$0.0	N/A
49	Lutera-28	Actavis	\$47.3	-6.0%	2,132.0	-10.0%	\$0.0	N/A	\$0.0	N/A
50	Amethia	Actavis	\$46.7	92.0%	259.0	>100.0%	\$0.0	N/A	\$0.0	N/A

Sources: Sales/TRx, IMS Health; DTC media spend, Nielsen; journals, Kantar Media.

Note: List includes contraceptives and products FDA indicates as approved for treating fertility, menopause and osteoporosis.



CLINICAL CORNER

Is the pharmaceutical industry sexist? This would seem counterintuitive for a business with so many female constituents. Yet, most clinical trials of blockbusters launched during the past two decades have been geared more toward males. The problem started when the FDA issued its General Considerations for the Evaluation of Drugs in 1977, effectively excluding women of childbearing age from trials, says Dr. Rose Blackburne, senior medical director in the general medicine therapeutic delivery unit at the CRO Quintiles, and a board-certified OB/GYN. The



Rose Blackburne

agency reversed course in the 1990s, mandating evaluation of gender differences in trials, but industry never quite came around.

"Gender-specific analyses are required to detect gender differences in effects of pharmaceutical and non-pharmaceutical interventions, but they are seldom performed," says Blackburne.

There are reasons. "There is always a concern for unintended pregnancy in any clinical trial," adds Blackburne, and "the discussion regarding reliable contraceptive during a trial can sometimes be daunting."

Another factor: gender bias as regards treatment for conditions such as heart disease (emergent treatment for acute MI), hip and joint replacement. In these areas, "it has been proven that women are treated far less aggressively," Blackburne adds, and thus "are also less likely to be offered the opportunity to participate in a clinical trial."

That bias contributes to medical challenges. For example, anti-retroviral medicines that treat HIV/AIDS have been studied mainly in men. But HIV drugs' efficacy and tolerability profiles often manifest differently in women, and side effects may be amplified.

As doctors, patients and manufacturers see the opportunity to re-evaluate products to better address symptoms that manifest in women more directly, the situation is changing. "Women's health itself is being redefined," says Dr. Lisa Dietrich, an EVP at Interpublic Group's ICC Lowe and an OB/GYN. She says the industry is expanding the definition to include conditions and diseases once thought to be, at best, gender-neutral, or, at worst, "only a man's issue."

In insomnia, for instance, after data demonstrated that zolpidem-based sleep aids are metabolized differently in women than in men, Dietrich says it led to a label change and updated dosing recommendations that are segmented by gender.

Blackburne sees the trend as an outgrowth of policies and guidelines issued in the latter 1990s and early 2000s that "further mandated the inclusion of women and minorities in clinical research."

Diagnostic guidance and pharmacologic treatment data are increasingly being stratified by female gender, notes Dietrich, and integration of services in women's health specialty centers is on the rise.

"Moreover," she points out, "the majority of healthcare providers over the next 10 years will be female, based on a medical school student analysis, with inherent impact on delivery of healthcare to women."



risk of diseases such as osteoporosis and colorectal cancer," recalls Dr. Lisa Dietrich, an OB/GYN and EVP of medical affairs at Interpublic Group's ICC Lowe. "Safety concerns now dominate practice patterns," she says. "Yet the efficacy is unsurpassed. So this does present an opportunity for a first-in-class product with a significantly better safety profile."

Osteoporosis, similar to HRT, sees burgeoning demand due to expansion of the older demographic, but safety has curbed that demand. The bisphosphonate category, while well-regarded by physicians as effective and safe, has suffered considerably over concerns of atypical fractures and osteonecrosis of the jaw (ONJ).

Patients also have been put off by the drugs' requirement to remain standing for a period of time after intake and potential for esophageal side effects. As a result, physicians have taken patients off of therapy after long-term usage as well as in advance of dental procedures. Adherence is less than 40% of the recommended dose due to the need to take pills at least monthly, says Jessica Jarvis, associate principal, ZS Associates.

Bisphosphonate concerns have opened an opportunity for Amgen's Prolia (denosumab), which targets a different protein (RANK ligand) responsible for bone loss. Approved in June 2010, denosumab is dosed bi-annually and has been a key growth driver in Amgen's portfolio. Sales more than doubled last year to \$472 million. "Prolia has the opportunity to expand beyond bisphosphonate failures and renally impaired patients to become the industry gold standard—especially if, over time, the quality of bone that is formed in the environment of reduced bone turnover is strong," says Dietrich.

Zuckerman cites a recent study published in *The Lancet*, where Prolia and Eli Lilly's bone-builder Forteo (teriparatide) were combined. The duo fostered greater increases in bone mineral density (BMD) in postmenopausal women with osteoporosis than either agent alone.

"Further down the line, we are going to see more combination use in osteoporosis," he predicts. "For women with considerable bone loss, this showed a significant change and boosted bone mass—they have not been able to show significance to this degree."

Merck—the osteoporosis category trailblazer, whose Fosamax bone drug had reached \$3 billion in annual sales before its patent expired in 2008—also is gunning for this market in an attempt to reclaim its leading status. Odanacatib offers a new mechanism of action in tackling bone loss due to osteoporosis.

By targeting the enzyme Cathepsin K (CatK), odanacatib is meant to stem the destructive activity of the osteoclast while preserving its ability to signal bone-building osteoblasts to perform their job, resulting in more physiologic activity. Odanacatib has been a highlight in Merck's pipeline, which has been under scrutiny by Wall Street.

However, management said it would be held back from regulators until more data could be obtained in a trial extension, stoking analyst concern that it might jump the tracks. Other companies' attempts to develop CatK-enzyme targeting therapies have ultimately fizzled due to dermatologic side effects.

Similar to menopause, companies who are in or poised to enter the osteoporosis space face hurdles. Jay Carter, SVP/director of strategy at AbelsonTaylor, cites an *NEJM* study suggesting only 13% of women aged 65 on Medicare get that baseline screening. Says Carter, "This may well become a public health issue in the next 10 years." ■

Noah Pines, an independent marketing research consultant, has done consulting work for companies referenced in this article.