

# Awakening the Silent Osteoporosis Market

Osteoporosis. The potential market is massive, and drugs offering new hope for patients, such as Forteo, are about to expand the industry's range of effective therapy to cope with the growing incidence of this condition. Now, physicians and patients must be made more aware of the need to identify and treat the condition. Here's a look at the current market and what lies ahead.

By Milton Liebman

**W**e've seen this therapeutic problem before — the need to treat a condition that shows no symptoms now but threatens serious consequences in the future.

That problem is being solved in dealing with cardiovascular disease. Hypercholesterolemia is a risk factor for myocardial infarction and hypertension poses threat of stroke, but cholesterol and blood pressure measurements are routine in physical exams, and, where indicated, therapy is initiated to lessen possibility of cardiovascular incidents.

Not so for osteoporosis. Osteoporosis is defined by the World Health Organization as a skeletal disease with low bone mass and deterioration of bone tissue, resulting in susceptibility for fracture. Gradual bone loss begins between ages 30 and 40. Osteoporosis is often called the "silent disease," because in early stages there are no symptoms. In the United States, roughly one in four women over age 50 has primary osteoporosis.

While industry has effective drugs to prevent and treat the condition, to provide needed therapy drug companies must help identify potential patients. Bone mineral

density scans predict the presence of osteoporosis, particularly in postmenopausal women, but these scans are not usually part of physical exams for many of these women, and no symptoms are evident. With bone density testing not routine, a fracture often is the first clinical evidence that osteoporosis is present — hardly a good diagnostic technique — and hence, one of the major problems facing pharmaceutical marketers and, of course, women.

Dr. Ethyl S. Siris, professor of clinical medicine at Columbia University College of Physicians and Surgeons, found that 46 percent of postmenopausal women have undiagnosed low bone mineral density. “I didn’t think that we were going to find that nearly half the women had low bone density,” Dr. Siris said. Data were collected from 200,160 women 50 years or older with no history of osteoporosis, and were seen in 4,236 primary care practices in the

public health problem. Prevalence data show there is now a total of 14 million men with osteoporosis and low bone density, and that figure is expected to grow to 17.3 million by 2010.

“Osteoporosis has emerged as a major clinical challenge for physicians ... related both to its prevalence and the morbidity and mortality of associated fractures,” according to the National Osteoporosis Foundation.

“Despite the fact that viable treatment options exist, a vast number of patients remain undetected until they experience their first fracture,” an analysis by the research organization Datamonitor states — a conclusion substantiated by key private and government agencies.

### Diagnostic dilemma

Osteoporosis is the most common metabolic bone disease in older people in the United States. Updated prevalence data released in February by the National

detection of osteoporosis and is an important guide to appropriate therapy.

The introduction of peripheral bone densitometers — which measure bone density in the wrist, heel, fingers, or forearm — may offer physicians a faster, less expensive means for detection. But, at this time, DEXA remains the “gold standard.” No organization currently advocates universal screening of all women — for the most part claiming that it is not cost effective. The screening test is reserved for women with independent risk factors and Medicare will pay the cost for these covered patients.

The normal risk factors include menopause and other estrogen deficiencies, vertebral abnormalities, and a range of thyroid conditions. Physicians take into account family history and unexplained back pain. An uncommon and interesting new diagnostic indicator was reported in the *Archives of Internal Medicine*, January 14. Fractures in premenopausal women between the ages of 20 and 50 were associated with a 74 percent increase in fractures after the age of 50. “Therefore this is an important clinical risk factor that points to the need for bone density measurement, consideration of lifestyle modification, and anti-osteoporosis therapies in these women,” according to the researchers.

Visits to physicians for osteoporosis reached 5.2 million for the year ending May 2001, according to IMS HEALTH data, almost double the number of four years ago. Sixty-one percent of visits were to primary care physicians, 16 percent to gynecologists, and 8 percent to rheumatologists. Sixty percent of the visits were by women age 65 or older. However, diagnosis rates remain comparatively low. Generally, there is a lack of awareness among women, as well as among physicians, in the opinion of Datamonitor, and the number of patients referred to radiologists for scans is low despite data showing benefits of a range of drugs in preventing

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United States. The participants were enrolled in the National Osteoporosis Risk Assessment study (NORA) funded by Merck (*JAMA*, December 12, 2001).

Accelerated bone loss is greatest in the first three to six years after menopause. It levels off, and then resumes premenopausal loss levels. Secondary osteoporosis results from use of medications and the presence of other disease conditions. In addition to women, one of eight men, or 2 million in the same age bracket, has osteoporosis. The incidence is lower because men have a larger bone mass. But medical authorities state that male osteoporosis is a prominent

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“Although osteoporosis is well defined and easy to diagnose, much debate exists around the question who and when to diagnose,” Datamonitor states. Dual Energy X-ray Absorptiometry (DEXA) is the most widely-used and highly-regarded diagnostic test. The test is critical to the

the onset of osteoporosis in high risk patients. The National Osteoporosis Foundation advocates scans for all women over age 65.

### Opportunity for DTC campaigns

Opportunities exist for manufacturers of preventive therapies to drive product sales by promoting disease awareness and diagnosis. Published reports of large clinical trials that show favorable results for drugs in preventing onset are likely to increase physician prescribing. Datamonitor analyst Jane Richardson emphasizes the need to encourage physicians to refer patients with one or more risk factors to radiologists for DEXA scans, and to initiate preventive therapy. If companies can produce cost

In the United States, 95 to 100 percent of women who are screened and diagnosed with osteoporosis receive treatment. Drug companies may find it worthwhile to drive diagnosis rates by developing DEXA scanning programs. Either on their own or in conjunction with community or other organizations, companies can support mobile osteoporosis testing units which travel to shopping malls, clubs for the elderly, county and state fairs, and other events, following the path taken by traveling blood pressure and cholesterol testing labs.

### Prevention and Treatment

With osteoporosis primarily linked to age, the best steps toward prevention are taken in youth, when individuals can develop peak

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effectiveness data that show the benefits of preventive therapy, she says, the case for convincing physicians to use their drugs will be stronger.

Pharmaceutical company drug advertising in professional journals stress the prevention of fractures as a goal. An ad for Actonel states, "... approximately one in five postmenopausal women who experience a vertebral fracture will suffer another vertebral fracture within just one year. Help stop the fracture cascade."

Direct-to-consumer ad campaigns can be used to raise consumer awareness. The advertising, either product or disease focused, would have the goal of sending women to discuss therapy with their physicians. Currently, such efforts are being made: twice in the same Fosamax consumer ad runs the statement, "ask your doctor about a bone density test."

bone mass. Good nutrition and exercise are key factors. In particular, adequate calcium and vitamin D are important and lifelong use of supplements often are recommended.

After menopause, antiresorptive drug therapy reduces and prevents excessive bone loss that leads to fragility. The end result is a positive effect on bone mineral density. The therapeutic agents include hormone replacement therapy (HRT) such as Premarin, selective estrogen receptor modulators (SERMs), specifically Evista, the bisphosphonates Fosamax and Actonel, and Calcitonin. Food and Drug Administration approval is expected this year for Forteo, a drug in a new class called parathyroid hormones (PTH). This anabolic therapy actively stimulates new bone formation. Developed by Eli Lilly, Forteo was approved by an FDA expert panel in July, and now awaits agency action.

A new bisphosphonate, Zomata, has been shown to suppress bone turnover and increase bone density in postmenopausal women for up to one year after a single intravenous injection. Now being developed by Novartis, it is in phase III testing.

Global sales for the total osteoporosis/menopausal disorders market in the year ending November 2001 were \$5.5 billion, according to research by IMS HEALTH (see Figure 1, page 61). This figure is expected to double by 2008.

### Dual benefits with HRT

Hormone replacement therapy helps prevent osteoporosis through its effects on bone degradation and also acts to control climacteric symptoms of menopause such as hot flashes and vaginal dryness. The HRT market is dominated by Wyeth's Premarin family of products which had global sales of \$1.8 billion in 2001, or 33 percent of the combined menopausal/osteoporosis market. Sales are expected to be at the same level this year. Premarin products had a growth rate of only 5.3 percent, low compared to other drugs, because it is a mature product line. It is estimated that sales will fall 20 percent to \$1.5 billion by 2008 from competition with non-hormonal drugs, according to Datamonitor.

Premarin was first launched in 1942. It received limited protection against competition when the FDA ruled in May 1997 that no synthetic product could be biologically equivalent. New dosage forms Premphase and Prempro, consisting of combinations of conjugated progestin and estrogen, were introduced in 1996. Premphase is sequentially combined therapy for use in premenstrual years. Prempro is a continuously combined dual hormone agent to which women can switch thereafter.

Prempro is used for the prevention of bone loss in postmenopausal women but is not approved for treatment due to lack of clinical trials showing prevention of fracture. It can cause side effects — bleeding,

bloating, and breast soreness. More important, there is concern about long-term use of HRT because of reported increase in risk of breast cancer, blood clots, and other serious conditions.

In response to the negative side effects, Wyeth is developing a much lower dose formulation of HRT. Studies have shown that the standard dose Prempro can be reduced by three-quarters and produce the same bone-maintaining benefits with a significant reduction in side effects.

The findings have been substantiated by the Woman's HOPE (Health, Osteoporosis, Progestin, Estrogen) study published in the June 2001 issue of *Fertility and Sterility*. Wyeth is expecting FDA approval of a low dose Prempro. It will provide new life to the Premarin family, and give Wyeth an opportunity to promote the improved version to physicians and the public. The goal is to maintain its leading role in the HRT-for-osteoporosis market.

### Non-hormonal therapy

The largest selling drug for prevention and therapy of osteoporosis is Fosamax (alendronate) from Merck. Fosamax was recommended by physicians for 37 percent of their patients, according to IMS HEALTH.

Fosamax was the first of the non-hormonal drugs called bisphosphonates and was introduced in 1995. Clinical trials showed that it could slow the rate of bone depletion, and after approval, it was also shown to be effective in *preventing* the condition. Fosamax and other bisphosphonates are generally considered more effective than HRT for osteoporosis therapy.

In 2001, sales of Fosamax increased to \$1.2 billion, with a market share of 34 percent. Datamonitor projects sales of \$1.5 billion this year. A new, once-weekly formulation of Fosamax was approved by FDA in October 2000, and it has been shown as effective as the once-daily dose. Fosamax must be taken on an empty stomach and the patient must remain

Figure 1

U.S. SELECTED OSTEOPOROSIS MARKET			
Prescription Sales Only			
Last 12 months ending Nov. 2001			
	Manufacturer	Total Sales \$*	% Market Share
<b>Total Selected Market</b>		<b>5,523,627</b>	<b>100</b>
<b>Bisphosphonates</b>		<b>1,947,695</b>	<b>35.3</b>
Fosamax	Merck	1,207,510	62.0
Aredia	Novartis	551,503	28.3
Actonel	Procter & Gamble	162,833	8.4
Didronel	Procter & Gamble	14,033	0.7
Zometa	Novartis	11,372	0.6
Total Others		444	0
<b>Estrogens</b>		<b>1,813,322</b>	<b>32.8</b>
Premarin	Wyeth	1,299,154	71.6
Climara	Berlex	85,652	4.7
Estrace	Warner-Chilcott	82,786	4.6
Vivelle-Dot	Novartis	53,812	3.0
Estraderm	Novartis	53,173	2.9
Total Others		238,744	13.2
<b>Estrogens/Progestones</b>		<b>913,799</b>	<b>16.5</b>
Prempro	Wyeth	728,096	79.7
Premphase	Wyeth	61,025	6.7
Femhrt	Parke-Davis	45,846	5.0
Ortho-Prefest	Ortho	32,188	3.5
Combipatch	Novartis	25,282	2.8
Total Others		21,362	2.3
<b>Bone Den. Reg. (SERMs)</b>		<b>555,403</b>	<b>10.1</b>
Evista	Eli Lilly	555,403	100
<b>Calcitonins</b>		<b>293,408</b>	<b>5.3</b>
Miacalcin	Novartis	293,400	100
Calcitonin-Salmon	AstraZeneca	8	0

\*Numbers are in thousands (000)s  
Source: IMS HEALTH

upright for 30 minutes afterwards — often a hardship for very old people. It is the only such medication for the condition to receive approval for a weekly dose. The patent on the original formula expires in 2003, but the once-weekly dose is protected until July 2018. Fosamax received approval for treatment of osteoporosis in men, opening another market of close to two million patients.

Fosamax faces competition in its class from Actonel (risedronate), marketed by Procter & Gamble (P&G) and Aventis, which received FDA approval for use in

osteoporosis in April 2000. The competitive advantages offered by Actonel are more rapid onset of action. It demonstrates a significant and consistent reduction in vertebral fractures in only one year of treatment, and it has a longer duration of response. Actonel also showed a five-year vertebral fracture reduction rate of 50 percent. These qualities give it an advantage over Fosamax. Though Actonel does cause upper GI problems, it has a better side effect profile than Fosamax, according to a Datamonitor analysis. A once-weekly form of Actonel is currently being developed by P&G and Aventis.

Sales in 2001, after eight months on the market, reached \$163 million, and this year the sales figure is expected to be \$259 million. By 2008, it is projected to become a billion-dollar product.

Among the new bisphosphonates in the pipeline, an NDA has been submitted for YM 175 (incadronate) from Yamanouchi. Bonviva (ibandronate) from Roche, is now in phase III trials.

The increased volume of data supporting the use of bisphosphonates has boosted the market share for the class to 28 percent. According to Dr. Ethyl S. Siris, bisphosphonates reduce the risk of fracture by 40 to 50 percent without estrogen side effects. They bind to bone to decrease or stop bone loss, she said, with only a minority of patients complaining of upper GI problems.

The relatively high side effects seen with HRT do not result from Evista therapy because of greater specificity of action. It appears to have benefits similar to estrogen in reducing bone loss and risk of spinal fracture, Dr. Siris told a press briefing sponsored by the AMA. It acts like estrogen in some parts of the body and blocks the effects of estrogen in other parts. Lilly is seeking approval for additional estrogen-related benefits such as prevention of breast cancer and protection against heart disease.

Evista competes against HRT and bisphosphonate therapy and Eli Lilly faces the task of promoting the advantages of its drug over both. "If Eli Lilly can receive approval for these additional indications, Evista will have a clear competitive advan-

### Patch it up

Unique drug delivery forms can be very useful and appealing, as exemplified by Estraderm (estradiol) from Novartis, which is indicated for osteoporosis. It was once the only patch and now is the top selling brand. Novartis has improved the product since it was launched in 1986 by making it smaller, thinner, more flexible, and less irritating than the original. It had sales of \$255 million in 2000. The market has become crowded and Estraderm faces competition from others, including Schering AG's Climara, which had sales of \$53 million in 2001.

Solvay is also focusing on HRT therapy. Estratab (esterified estrogens) and Femoston (estradiol and dydrogesterone), both have osteoporosis indications. It is also developing an estrogen and progestin patch, now in phase III trials. There are other companies developing variations of HRT products, only some of which will have osteoporosis indications.

### And then there's Calcitonin

Calcitonin is a medication used with calcium and vitamin D supplements in management of postmenopausal osteoporosis, and it is available as a nasal spray or an injection. Miacalcin is a calcitonin nasal spray from Novartis. It had sales of \$293 million in 2001. Clinical studies to demonstrate the effectiveness of *salmon* calcitonin in decreasing the risk of fractures have been spotty. The product is widely perceived as being less efficacious than alternatives, according to Datamonitor, but still has a role in therapy.

Unigene Laboratories' Forcaltonin (recombinant salmon calcitonin) nasal spray completed phase III trials and the company has injection and oral forms in earlier clinical testing stages.

### New hope for patients

Forteo (teriparatide), the first in a new class of drugs known as parathyroid hormone

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### SERM: different estrogen action

Eli Lilly is marketing Evista (raloxifene), the first selective estrogen receptor modulator (SERM). It was launched in January 1998 for prevention of osteoporosis and was approved for treatment in September 1999. With both indications, sales of Evista jumped 60.5 percent to \$522 million in 2000 and \$555 million in 2001. That's 10 percent of the market for this single drug, as calculated by IMS HEALTH. Sales this year are expected to reach \$939 million, but are expected to fall off in the years following due to competition from newer SERMs.

tage," Datamonitor says. Thus far, clinical studies show these benefits.

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(PTH), awaits release by the FDA. An expert advisory panel unanimously voted in July 2001 that the drug be approved for treating osteoporosis in postmenopausal women. It received a split decision on whether it should get an indication for osteoporosis in men. The drug is the first anabolic agent for osteoporosis.

Forteo offers new hope to osteoporosis patients since it is capable of increasing bone density rather than just suppressing bone degeneration. The anabolic drug stimulates osteoblasts responsible for bone formation by making them live longer. Current drugs function by slowing osteoblasts responsible for bone degeneration. Forteo reduces vertebral fractures by

promoting two products for the same indication to the same physician base.

A striking report of results with Zometa (zoledronic acid) appeared in the *New England Journal of Medicine* (Feb. 28, 2002, pg. 653). The new bisphosphonate was administered as a single intravenous dose to 351 postmenopausal women at three-month intervals up to one year.

It was found that "infusions given at intervals of up to one year produce effects of bone turnover and bone density as great as those achieved with daily oral dosing with bisphosphonates, with proven efficacy against fractures," said the report of the study team led by Ian R. Reid, M.D., professor of medicine and

of solid tumors. The osteoporosis study was to establish dosage as part of phase II trials. Novartis has now embarked on a phase III for treatment of osteoporosis and other metabolic bone disorders with approximately 11,000 patients at 400 participating centers.

Over the next 10 years a slow trickle of pipeline products, including other PTHs, will reach the market. NPS Pharmaceuticals' recombinant parathyroid hormone ALX1-11 is currently in phase III clinical trials, and results from earlier studies have been positive. Merck is conducting trials of ALX1-11 in combination with Fosamax. Inhale Therapeutic Systems has an inhaled PTH in phase I.

Servier is assessing the potential for S12911 to stimulate bone formation in phase III trials. It is a strontium reneate. There are other agents in earlier phases of study, and these products are expected to be used primarily for treatment of moderate to severe osteoporosis patients who have had one fracture and are candidates for additional ones.

GlaxoSmithKline bought the development and marketing rights from Germany's Bayer AG for one of new class of drugs, PPAR-gamma modulators, now in preclinical testing. The drug, Bay 54-9801, forms new bone in animal models of osteoporosis.

The prevalence of osteoporosis is expected to increase. Datamonitor foresees a growth in the population in the United States from the current 10 million to 11.9 million in 2008. Worldwide, the number is expected to increase from 42.8 million to 47.3 million cases. A growing awareness of osteoporosis and increased funding for DEXA scanning are predicted, increasing the likelihood of earlier diagnosis. The need for the growing number of products is clear. ■

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more than 60 percent and non-vertebral fractures by more than 50 percent. It is administered by self-injection daily during an 18-month course of treatment. Though well tolerated by the majority of test subjects, the labeling will note the occurrence of bone malignancies for life-long dosages of PTH. However, in clinical trials, no case of bone cancer occurred with test patients.

Forteo is expected to be positioned as a remedy for severe osteoporosis which would lessen competition with Evista for market share. Also, Lilly will benefit by

endocrinology, University of Auckland, New Zealand. He concluded that an annual infusion "might be an effective treatment." An increase in spine mineral density of 5 percent achieved at 12 months was similar to that produced by a daily 10 mg dose of aldrionate (5 percent), a daily 5 mg dose of risdrionate (3 percent) or a daily 150 mg dose of pamidronate, (1 percent).

Zometa was approved first by the FDA for treatment of hypercalcemia of malignancy. On February 22, it was approved for multiple myeloma and bone metastases

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