



COX-2 INHIBITORS

by Virginia Kirk

A THERAPEUTIC PATH TO SUCCESS

Celebrex and **Vioxx** have taken considerable patient share from classic NSAIDs in the past two years, but they will soon **have to compete** with second-generation Cox-2 inhibitors

The marketers of Cox-2 anti-inflammatory drugs, have enjoyed two years of record-breaking sales, but with new products poised to come to market, the challenge will be to hold onto their strong positions.

Cox-2 inhibitors entered the market with a splash with the launch of Celebrex in 1998. The Pharmacia/Pfizer co-marketed arthritis pain medication is now the No. 6 selling prescription medication in the United States. Six months later, Merck & Co.'s Vioxx entered the market, and is now selling just slightly less than Celebrex, holding the No. 14 position.

Celebrex and Vioxx have taken considerable patient share from classic NSAIDs over the past two years, but they face a challenge from second-generation Cox-2 inhibitors making their way through the pipeline. Merck and Pharmacia/Pfizer each are working on a second-generation of Cox-2 inhibitors, with Novartis planning its own entry. Pharmacia/Pfizer's valdecoxib should go before the Food and Drug Administration for approval early next year, says Pharmacia spokesman Craig Buchholz. At Merck, the NDA for Arcoxia (etoricoxib) should be filed later this year. And Novartis' product, COX189, is in Phase II

clinical trials for treating osteoarthritis, rheumatoid arthritis, and pain.

Of the therapies in development, the most advanced is valdecoxib, which is preregistered in the U.S. and in preclinical development in Japan. Analysts predict peak-year sales of valdecoxib in the range of \$500 million to \$750 million.

"As far as we can tell from the scant data released by the pharmaceutical companies, it appears the companies are working on follow-up products that would have advantages over current products," says Kat Neumeyer, research analyst with Mosaic at Decision Resources Inc. "In the case of Merck, that means it would look for a rheumatoid arthritis approval while Pharmacia/Pfizer would likely seek an indication for acute pain in its next product."

Merck also is looking to expand Vioxx's indications to include rheumatoid arthritis, colon polyps, and Alzheimer's disease.

Ms. Neumeyer says analysts at her company are predicting that the new Cox-2s might come out with fewer gastrointestinal side effects, but no more improvement in pain management. And analysts believe that the next-generation of Cox-2 inhibitors will be priced lower than Vioxx and Celebrex.

"They'll have to do that or they'll never expand the market," she says.

Merck is vying with Pharmacia and Pfizer for osteoarthritis market leadership. Currently, Merck has the edge in Europe thanks to Vioxx's earlier launch, while Pharmacia and Pfizer command more of the U.S. market as a result of a huge promotional push behind Celebrex. Each company's advantage will gradually erode, however, as the near-equivalency of their Cox-2 inhibitors is borne out.

According to Decision Resources, the market for osteoarthritis drugs totaled \$2.9 billion in 2000. During the course of a 10-year forecast period, factors influencing pharmaceutical sales will include the availability of numerous Cox-2 inhibitors, the continuing decline in classic NSAID use, and the availability of chondroprotective agents. Analysts predict that the most likely overall impact on the market will be a moderate increase by 2010.

Decision Resources recently completed a study on osteoarthritis that looked at the competition between the two marketed Cox-2 inhibitors and pointed to price as the stumbling block for sales growth in Europe. The report also concludes that after nearly two years of availability, there are significant unmet needs in the treatment of osteoarthritis.

The growth in sales and high projections for future sales come despite the fact that the Cox-2s do not clinically improve the treatment for osteoarthritis more than earlier therapies, such as NSAIDs, the report points out. However, since higher dosages of Cox-2s can be taken and the gastrointestinal side effects, such as ulcer related symptoms, are lower, they have become popular with patients. One long-term study on Pharmacia's Celebrex found that the likelihood of gastrointestinal problems was 2.9% in osteoarthritis patients taking NSAIDs versus 1.4% in patients taking celecoxib, the active chemical in Celebrex.

"Both Merck and Pharmacia/Pfizer recently put out reports saying both agents missed their sales targets for the first two quarters of this year," Ms. Neumeyer says. "That was essentially what we predicted. But, we don't think sales will plateau."

Ms. Neumeyer says more entries in the market will lead to the "classic end-set market" unless a company can figure out a way to produce a less expensive version.

Hemant K. Shah, an analyst and head of HKS & Co., in Warren, N.J., says he does not expect the Cox-2 inhibitors to gain more than 45% of the pain-relief market. They currently hold about 41%.

Vioxx and Celebrex heavily promoted to managed care

According to Cognet-X's PAR-Rx Report, the top 10 prescription medicines most heavily promoted to managed-care pharmacy directors during the first six months of 2001 were:

Source: Cognet-X Inc., Feasterville, Pa.

Amid intense competition, three proton pump inhibitors were the most heavily promoted prescription brands to managed-care pharmacy directors, according to Cognet-X Inc.'s Promotional Assessment Research Report, also known as the PAR-Rx Report.

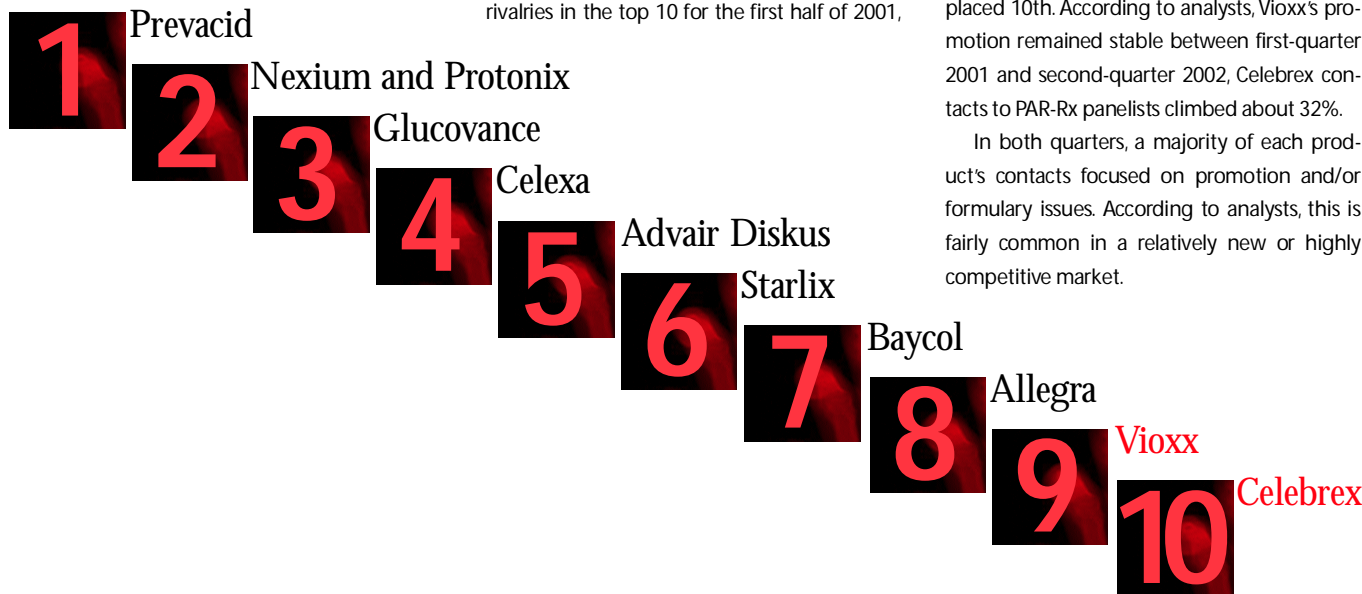
Other therapeutic categories with close rivalries in the top 10 for the first half of 2001,

include oral diabetes agents and the pain-relieving class known as Cox-2 inhibitors.

Cox-2 inhibitors are defined by Celebrex, which is co-marketed by Pharmacia and Pfizer, and Vioxx, which is marketed by Merck & Co.

In the first six months of 2001, Vioxx pushed past Celebrex. Vioxx was ranked ninth; Celebrex placed 10th. According to analysts, Vioxx's promotion remained stable between first-quarter 2001 and second-quarter 2002, Celebrex contacts to PAR-Rx panelists climbed about 32%.

In both quarters, a majority of each product's contacts focused on promotion and/or formulary issues. According to analysts, this is fairly common in a relatively new or highly competitive market.



Percent of Chronic Pain Patients Treated with Different Drug Classes

	Mild OA	Moderate OA	Severe OA	Lower Back	Neuropathic
Acetaminophen	44%	33%	27%	28%	23%
OTC NSAIDs and/or aspirin	34	27	22	27	20
Prescription NSAIDs (excluding Cox-2s)	25	36	39	38	31
COX-2 INHIBITORS (CELEBREX AND VIOXX)	17	29	37	26	20
Other non-narcotic prescription analgesics	9	12	15	13	16
Muscle relaxants	8	10	14	24	16
Narcotic prescription analgesics	6	12	24	17	23
Tricyclic antidepressants	4	7	12	14	28
Anti-seizure medications (Neuontin, etc.)	3	4	8	8	30
Corticosteroids	2	5	9	5	9

Source: Cognet-X Inc., Feasterville, Pa.

have criticized the JAMA article's analysis of several studies as "flawed and unsound." They contend the study had no new clinical information and was based on an inappropriate re-analysis of several older clinical studies containing data that were not suitable for combination and comparison. Patients in these studies had different underlying diseases and different cardiovascular risk profiles.

Merck spokeswoman Jan Weiner says when Merck was before an FDA advisory committee earlier this year for an unrelated label change, it presented several studies related to cardiovascular effects.

"We pulled all the commonly used NSAIDs related to platelet effects and showed how Vioxx fit on that spectrum," Ms. Weiner says. Merck's data reflected that naproxen, if taken every 12 hours blocks platelet aggregation — an effect similar to aspirin — but not seen in other NSAIDs and did not indicate anything in Vioxx that actually increases the chance of cardiovascular protection.

"We also presented the results of a medical analysis we had done in which we looked at three different sets of studies: those in which we compared Vioxx with a placebo, to non-naproxen NSAIDs, and those comparing Vioxx with naproxen," she says.

Ms. Weiner adds: "Our analysis found no difference in the cardiovascular rates in the studies versus the placebo and the non-naproxen NSAIDs. The company has additional studies ongoing and we'll continue to evaluate that data."

Heavy Promotion May be Cause for High Sales

Vioxx and Celebrex were the ninth and tenth most-highly promoted prescription medicines to managed-care pharmacy directors in the first half of 2001, according to research by Cognet-X Inc., a pharmaceutical

research, consulting, and software development company.

In the second quarter of this year Pharmacia/Pfizer increased the promotion of Celebrex to capture 62% of the promotional share of voice while Vioxx, keeping the same level of support, saw its share of voice drop to 38% from 45% in the first quarter of 2001.

"Celebrex used a non-GI focus which helped them have a very successful launch," says Mark Temples FCB senior VP and managing supervisor. "Vioxx based its campaign on its efficacy. Patients are concerned about safety, but efficacy is a big issue. It's not just tolerability versus the other NSAIDs."

FCB HealthCare is the professional advertising agency for Vioxx.

Bebe Barber, associate creative director at FCB adds, "Efficacy remains our primary differentiator. Vioxx is a once-a-day product and we have excellent clinical trials that demonstrate efficacy and that is the main differentiator between these two Cox-2s."

Consistency of message was FCB's other strong point for the campaign, Mr. Temples says. "We hit on a good way of presenting the product and we have been true to that."

Recently, Grey Healthcare Group Inc. was awarded the Celebrex global and U.S. professional advertising account.

Pharmacia and Pfizer co-market Celebrex in the U.S. and most international markets. Celebrex was the fastest-growing of the top 10 best-selling pharmaceutical products last year.

"We're thrilled to be working with Pharmacia and Pfizer, and to be able to implement the agency's creativity, strategic thinking, and innovative approach to global branding on behalf of Celebrex," says Jane Parker, president of GHG. ♦

PharmaVoice welcomes comments about this article. E-mail us at feedback@pharmalinx.com.

Experts on this topic

BEBE BARBER. Associate creative director, FCB HealthCare, New York; FCB is a global healthcare advertising agency

CRAIG BUCHHOLZ. Director of public relations, Pharmacia Corp., Peapack, N.J.; Pharmacia is a global pharmaceutical company

JUDY DROAR. VP, Market Measures Interactive L.P., Livingston, N.J.; Market Measures Interactive, a NOP World Health company, is a leading supplier of primary research to the global healthcare community

COGNET-X INC. Feasterville, Pa.; Cognet-X offers the pharmaceutical industry market research, consulting, and software development services that help companies build and refine their relationships with numerous customer bases, including the managed-care community

KAT NEUMEYER. Research analyst, Decision Resources Inc., Waltham, Mass.; Decision Resources provides a range of products and services to executives in the pharmaceutical, biotechnology, diagnostics, and managed healthcare industries, including primary and secondary research publications, multiclient advisory services, and customized consulting

JANE PARKER. President, Grey Healthcare Group, New York; Grey Healthcare is a global healthcare advertising agency

HEMANT SHAH. Analyst, HKS & Co., Warren, N.J.; HKS is an analyst company serving the healthcare industry

MARK TEMPLES. Senior VP, management supervisor, FCB HealthCare, New York; FCB is a global healthcare advertising agency

JAN WEINER. Executive director for communications for U.S. human health division, Merck & Co. Inc., Whitehouse Station, N.J.; Merck is a global pharmaceutical company