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How Drug Directory Helps Raise Tab for Medicaid and Insurers

They Pay for 'Off Label' Uses If Listed -- And Drugdex Lists Great Many of Them

By DAVID ARMSTRONG | Staff Reporter of THE WALL STREET JOURNAL

Alarmed by surging outlays for the drug Neurontin, Oklahoma's Medicaid agency last year sifted through patient records for clues. It found widespread prescriptions of the drug for uses not approved by the Food and Drug Administration.

Ninety-four percent of prescriptions for the Pfizer Inc. medicine were for these "off label" uses, the agency estimated, tripling its bill for the drug to \$3.7 million from its 1998 level. The state pondered whether to curb payments for off-label uses but quickly concluded there was little it could do.

That's because nearly all of the off-label uses for Neurontin were listed in the Drugdex Information Service -- a little-known publication that has quietly become a powerful reason for rising drug costs.

Published online by Canada's Thomson Corp., Drugdex is one of three federally recognized directories for authorizing coverage under Medicaid, the federal-state insurance program for the poor and disabled. Medicaid payment for an off-label prescription can't be denied if the condition being treated is listed under the drug's name in any of the directories. At least 31 states also compel private insurers to cover some or all of the off-label uses listed in the directories, according to health-care researcher Verispan LLC.

Drugdex's listings are far more extensive than those of the other two guides -- making it the de facto standard-setter in authorizing payment for unapproved uses of prescription drugs. Such uses, recent studies suggest, account for 40% to 50% of all drug use. That translates into significant revenue for the pharmaceutical industry, which relies heavily on government and private insurance to support the \$194 billion in annual sales of prescription drugs.

As government and employers see their drug tabs surge, more concerns are being raised about the efficacy and safety of so many prescriptions for treatments the FDA has never endorsed. Critics say the broad listings in Drugdex are a boost to drug-company efforts to get doctors to prescribe brand-name medicines for off-label uses. If insurance coverage didn't exist for these uses, they add, patients might take cheaper generic drugs, over-the-counter medicines, or nothing at all, saving the health-care system huge sums.

Michael Soares, director of editorial services for Micromedex, the Thomson unit that publishes the directory, says, "It is up to Medicaid to set the policies for what is reimbursed." He acknowledges that Drugdex's listings are wider than those of the other two directories, saying that reflects its larger staff, its effort to review more of the scientific literature and **its desire to reflect what doctors are actually prescribing.**

"Patients should not have effective, even life-saving, off-label-use drug therapies withheld from them simply because they are not reimbursed," Mr. Soares says.

Beyond Neurontin's two FDA-approved uses for epilepsy and pain related to shingles, Drugdex lists 48 other "therapeutic indications," or uses, for the drug, including bipolar disorder and other mental illnesses, headaches and hiccups. AHFS Drug Information, one of the other guides, lists only seven. The third guide, U.S. Pharmacopeia, lists

just one.

It's a broad pattern. Drugdex carries 203 off-label uses for the dozen top-selling drugs in the U.S. -- including Eli Lilly & Co.'s Zyprexa, Pfizer's cholesterol drug Lipitor and GlaxoSmithKline PLC's antidepressant Paxil. Drug Information carries only 68; U.S. Pharmacopeia, nine.

Drugdex publisher Thomson, the only private company to own one of the three guides, receives substantial revenue from the big drug companies that benefit from Drugdex listings. The company says that doesn't influence what Drugdex publishes. Similarly, Drugdex's status as an insurance authenticator "has no influence on us," Mr. Soares says.

Critics say Drugdex's criteria aren't strict enough. Drugdex often lists off-label uses based on one-patient observations or on studies that don't use the strict protocols of the FDA. And it **sometimes disregards evidence showing that off-label uses aren't effective.**

Arthur Levin, a member of the FDA's Drug Safety and Risk Management Advisory Committee, says that "simply being listed in a compendium" as a standard for coverage "makes no sense to me. It is overly permissive." Mr. Levin, who also runs the Center for Medical Consumers, a New York-based patient advocacy group, contends that **"most often the evidence for off-label use isn't there."**

Although drug companies are prohibited from promoting off-label uses, doctors can prescribe any FDA-approved drug for any ailment. One big reason for rising off-label use is patient demand. Many insurers liberalized their coverage standards for off-label uses in the early 1990s when desperate AIDS and cancer patients were dissatisfied with standard treatments.

The American Medical Association supports insurance coverage for any off-label prescription that represents "safe and effective therapy," as long as doctors pay attention to the scientific evidence and medical opinion. Off-label prescribing is "frankly just a way of life," says Edward Langston, an AMA board member and family physician in Lafayette, Ind., who says at least 10% to 15% of the prescriptions he writes are for off-label uses. "Patients would suffer without it."

Others say this standard is too lax. **"If you go to Drugdex, they will include every use that has ever been written about for a drug,"** says Larry Sasich, a pharmacist and former outside editor for Drugdex, who now works for Public Citizen, a Washington advocacy group that typically looks for ways to broaden Medicaid coverage. "I'm not saying they do a bad job. They do what they advertise they are doing. But **to use that as a standard to make reimbursement decisions is irresponsible."**

Keeping Out Many Uses

Drugdex said it is selective in its listings and doesn't include every potential off-label use of a drug. In the case of Neurontin, for instance, Mr. Soares said the drug is the subject of 1,326 articles, but Drugdex has cited only 169 of them and didn't list many off-label uses cited in those additional articles. And in a small number of cases when Drugdex lists an off-label use, it rates the drug as "ineffective" for the condition.

FDA Commissioner Mark McClellan has said he wants to see more off-label uses subjected to the FDA approval process. "It is not the same kind of definitive evidence we would like to see," he said in an interview this summer. "I'd like to figure out a better way to get more information on the label."

Officials at several of the state agencies that dispense the \$30 billion in annual Medicaid prescription outlays are searching for ways to control off-label spending. But Robert Reid, who runs pharmacy services for Ohio Medicaid, says he is unlikely to deny payment for an off-label prescription if there is a supportive reference in a directory -- even when the state doesn't think the use is warranted. If the patient appealed, "we would probably lose," he says.

A suit brought by a former Parke-Davis employee against Pfizer in U.S. district court in Boston seeks to recover some of the \$421.6 million the suit says Medicaid spent on off-label use of Neurontin between 1994 and mid-2000. The Justice Department-backed suit alleges that Parke-Davis, which Pfizer acquired in 2000 in taking over Warner-Lambert Co., illegally marketed the drug for off-label uses.

Pfizer has denied responsibility for the alleged marketing activities because they occurred before it acquired Parke-

Davis. But it has also raised another defense: Because the off-label uses were listed in Drugdex, the government has no right to recover anything after 1997 when the directory became an official verifier. "You have to show the claims were for a use not in Drugdex," argues James Rouhandeh, a Pfizer attorney.

Is this true?

Before 1990, state Medicaid agencies decided on their own whether to cover off-label uses. But after an outcry from cancer and AIDS patients and their doctors that year, lawmakers took control of the process. Following an evaluation by the agency then overseeing Medicaid, Congress barred the states from denying coverage for a drug if the use was approved by the FDA or supported by a citation in one of three drug directories then operating.

Congress overcame concerns that the compendia would face pressure from the drug industry because all three publishers were controlled by nonprofit associations, says George Silberman, an Elm Services Inc. health economist who, while at the General Accounting Office, helped draft the bill.

But later, one of the nonprofit guides went out of business. In 1997, Congress named Thomson's Drugdex as an official reimbursement source. Thomson says it sought the designation to gain equal status with competitors. Drugdex says it applies the same standards to off-label listings today as it did then.

The three directories share similar, encyclopedic formats describing how a medicine works, its chemistry, dosing guidelines and side effects. But Drugdex covers about twice as many medicines as the others and is the only one whose editorial decisions are made by a for-profit entity. At AHFS Drug Information, a nonprofit association of hospital druggists, decisions are made by the American Society of Health-System Pharmacists. Another nonprofit, the U.S. Pharmacopeial Convention, elects and appoints 325 scientists and practitioners to make the calls in its U.S. Pharmacopeia.

Thomson's scientific and health-care division, which includes Drugdex, accounted for \$780 million of the company's \$7.8 billion in revenue last year. One of the division's biggest operations is running "continuing medical education" seminars for the pharmaceutical industry. Thomson doesn't disclose medical-education revenue. But Physician's World, one of its units pursuing this business, had revenue of \$110 million last year, according to industry journal Medical Marketing & Media.

Thomson's medical-education customers include numerous companies whose drugs are listed in Drugdex -- including Pfizer, Glaxo and Lilly. Off-label uses of drugs are a frequent topic at medical-education seminars, which doctors often attend to fulfill state continuing-education requirements.

In its 2002 annual report, Thomson said its strategy in acquiring Physician's World and Gardiner-Caldwell, a similar company, was to "leverage" its other medical products in the medical-education market.

Mr. Soares says Drugdex makes decisions on off-label uses free of pharmaceutical-industry influence. "We would never risk any information business or the integrity of a product line for a leg up in another area," a Thomson spokeswoman adds.

Available only in online format, Drugdex appears to be eclipsing its two rival guides, traditionally available only in book form. Thomson over the last several years has noted the growth of its online-health data products and singled out Drugdex for special mention in 2000. The nonprofit group responsible for U.S. Pharmacopeia, by contrast, was having trouble making ends meet in 1998 and sold the publishing rights to the book to Thomson, while retaining editorial control.

Thomson won't discuss Drugdex pricing, but a salesman for the company quotes an annual subscription at \$3,823.

The U.S. Pharmacopeia book, used in many pharmacies, goes for \$164, or \$199 in CD form. Drug Information sells for \$185; a more recent Internet version is \$2,990 a year.

The three guides, whose primary audience is pharmacists, each have staffs of pharmacists, doctors and other medical professionals that review medical literature and conference presentations for possible new drug uses. But their views vary on the kind of research that qualifies as supporting evidence.

U.S. Pharmacopeia gives top points to clinical trials where patients are randomly assigned to take either a drug or a placebo, and where neither researchers nor subjects know who's in which group. It gives fewer points to studies that don't have control groups and to observational reports of a patient's response to a drug.

The American Hospital Formulary Service, which controls the AHFS Drug Information guide, says it looks for at least one, and often two randomized, double-blind and controlled studies before listing an off-label use.

These practices mirror FDA guidelines for evidence on new-drug approvals, which also give weight to larger numbers of studied patients.

At Drugdex, Mr. Soares says an article that justifies an off-label listing is one that is "reflective of a practice pattern and provides valuable insight to the clinician." Staffers are trained to know the difference between case studies and controlled trials. They place a higher value on certain studies, but also consider what was studied, the results and "what the value to the clinician will be," he says.

Support citations for Drugdex's off-label listings contain frequent examples of studies that don't involve control groups, of **single-patient observations** and of "open label" studies in which patients know which drug they are getting. Drugdex also supports some uses that were rejected by the FDA when the drugs' makers applied to have them approved. Mr. Soares says Drugdex includes such information as an aid to clinicians, and that they know the difference between the types of studies it cites.

One drug widely prescribed off-label is Botox, made by **Allergan Inc.**, and approved by the FDA for treating wrinkles, the involuntary contracting of neck muscles and certain eye conditions. Beyond those, Drugdex lists 38 off-label uses, including the treatment of tension headaches, for which it is rated "effective." U.S. Pharmacopeia lists nine off-label Botox uses; AHFS Drug Information carries none.

In support of its Botox listing for tension headaches, Drugdex cites five studies. Two, the directory notes, showed negative results for effectiveness, but the other three "reported statistically significant reductions in headache pain." Two of the positive studies, published in European medical journals, were small, open-label trials, one with nine patients and the other with 10. The third positive study compared Botox with a steroid treatment in a group of 20 patients.

Drugdex doesn't mention that one of the studies it cites showing negative results was conducted at a higher research standard -- a randomized, placebo-controlled and double-blind study. Another study, unmentioned by Drugdex, was also conducted at this higher standard and found Botox to be ineffective in reducing headaches. As for why it excluded the second randomized study of Botox, Drugdex said it already listed one such study showing a lack of efficacy and that the authors of the second study "appear to be questioning" their own results.

The best-selling arthritis drug Bextra, a Pfizer product, is listed in Drugdex as effective for postoperative pain -- a use that doesn't appear in the other two indexes. Drugdex cites three 2001 studies as support, covering patients undergoing oral and foot surgery and hip replacements. The studies were conducted by the developer of the drug, Pharmacia Corp., which Pfizer acquired last year.

The FDA in November 2001 rejected the company's request to label Bextra as a treatment for acute pain, which is often equated in drug trials with post-operative pain. The FDA said the studies were "inadequate to establish safety and efficacy." A Pfizer spokeswoman wouldn't say whether the studies Drugdex cites were among those considered by the FDA. Drugdex says its staff of clinicians assessed the studies and found that Bextra was shown to be effective.

Neurontin, the drug that was a red flag to Oklahoma, is FDA-approved as an adjunctive, or add-on, treatment of partial seizures for epileptics and for postherpetic neuralgia, a painful complication of shingles. In listing 48 off-label uses, Drugdex calls Neurontin effective or possibly effective for 46 and ineffective for two.

The off-label uses include treatment of cocaine addiction and social phobia, or the fear of socializing. Many of the citations in support of the listings, as disclosed in the guide, involve a single person's experience with the drug, or otherwise fall short of the highest research standards. The listings also omit some studies that found Neurontin was ineffective for the off-label uses Drugdex carries.

One, a 1999 study funded by the National Institutes of Health, found Neurontin had about the same effect as a placebo when used as the primary treatment for bipolar-disorder patients previously resistant to other therapies. In a 2000 study, funded by Parke-Davis, a placebo was more effective than Neurontin when used as an adjunctive therapy. The company study said results "did not demonstrate" that Neurontin was effective as an adjunctive bipolar treatment.

Drugdex said it hasn't cited these studies in its Neurontin section because it was unaware of them. After reviewing them, Mr. Soares said they were flawed and wouldn't be added. Drugdex said the Parke-Davis study indicated that eight of 47 patients may not have been taking Neurontin as directed, potentially skewing results. The second study, Drugdex said, involved only 31 patients -- which it said was too small to be meaningful.

Many More 'Flaws'

Terrence Ketter, a Stanford University professor of psychiatry and co-author of the NIH study, said that "there are a hell of a lot more flaws" in Drugdex's policies than in his study, including "using uncontrolled data and endorsing something that is patently wrong." He added, "There is no way you can justify" including noncontrolled data "if you are excluding controlled data."

One of the six authors of the Drugdex section on the uses of Neurontin, Nina Graves, has had a long association with Neurontin's maker, Parke-Davis. According to Parke-Davis records produced by Pfizer in the Boston lawsuit, Ms. Graves, a former University of Minnesota pharmacy professor, traveled extensively on behalf of Parke-Davis speaking about Neurontin. Through 1997, according to the records, she received at least \$75,000 in payments from the drug maker.

Ms. Graves, who now works for a medical-products company, declined to discuss her relationship with Parke-Davis or Drugdex. The Drugdex directory doesn't disclose any link between Ms. Graves and Parke-Davis or Pfizer online.

Thomson says Ms. Graves reviewed the original monograph, or passage, on Neurontin in the early 1990s. It says it was unaware of any association she might have had with the drug's maker.

Until a few weeks ago, Drugdex was the only guide that had an industry advisory board. It reviewed passages on specific drugs, though it didn't have a final say on what did or didn't get printed. After inquiries began for this article, Drugdex spokeswoman Jackie Reed said the industry advisory board "just recently has dissolved." Drugdex's Mr. Soares said the board was disbanded "because we want to get away from any look of impropriety."

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