

# Febuxostat, Allopurinol Jockey for Role in Gout

BY MITCHEL L. ZOLER

Estimates of how many patients with gout should be treated with febuxostat range from just 5% to millions, according to experts interviewed for this article.

What is not debatable 6 months after febuxostat went on the U.S. market is that it's clearly the second-line agent behind allopurinol, those same experts agreed. Allopurinol retains the top spot because of its substantially larger and longer track record and its dramatically lower cost.

Febuxostat received a warm welcome from gout specialists following its approval by the Food and Drug Administration. They cheered the arrival of the first new gout drug in decades, and early U.S. sales numbers for the drug were in line with expectations of Takeda Pharmaceuticals North America Inc., the company that markets febuxostat (Uloric), said Heather Dean, Takeda's marketing director for the drug. Several gout experts interviewed for this article said that they had no special concerns about febuxostat's safety, aside from the usual uncertainties that surround any drug when it first enters the market.

Despite that, the type of gout patient who is a good candidate for febuxostat treatment remains controversial. At one end are some experts who concede a scant few percent of gout patients—those who are truly intolerant of or unresponsive to maximum allopurinol treatment—as appropriate candidates. At the other end are specialists who say that febuxostat is the preferred drug for any gout patient who has moderate renal failure or who fails to respond to 300 mg/day of allopurinol, categories that encompass a sizeable fraction, perhaps even a majority, of symptomatic gout patients.

Some of the following facts that play into the decision to treat with allopurinol or febuxostat are undisputable:

- ▶ Allopurinol (or more accurately, its active form in blood, oxypurinol) is excreted by the kidney, so patients with impaired renal function have higher blood levels of oxypurinol than do patients with normal kidneys, a situation that demands dose adjustment when allopurinol is administered to patients with renal dysfunction.
- ▶ Allopurinol is ineffective at the standard dosage of 300 mg/day for perhaps half of gout patients, but in the vast majority of these cases it's effective when the dose is raised; some specialists are willing to prescribe the labeled maximum dosage of 800 mg/day. On the other hand, many physicians, even those who treat lots of gout patients, are not comfortable prescribing such high doses.
- ▶ Febuxostat does not require any dosage adjustment in patients with renal impairment, and is labeled for use only at either 40 mg or 80 mg/day.
- ▶ Internet-based drug stores sell febuxostat at a cost of more than \$5/day, compared with an Internet cost as low as \$0.10/day for allopurinol.

But much of the split on how gout patients will do on allopurinol and what fraction of them needs febuxostat depends on opinion.

Impaired renal function is an issue in gout because in addition to joints, kidneys are the place where uric acid crystals form. It's also hypothesized that hyperuricemia itself may cause kidney damage. As a result, "about half the patients with chronic gout have significant

impairment of renal function," said Dr. Peter A. Simkin, a rheumatologist at the University of Washington in Seattle.

Some experts, like Dr. Simkin, don't see impaired renal function as a barrier to allopurinol use. "It's both safe and appropriate to use allopurinol in patients with renal insufficiency," he said in an interview. "The main thing [renal insufficiency] means is that patients can often be properly controlled with a low dose

of allopurinol. Renal dysfunction is not a reason to not use allopurinol. You start with a low dose and escalate slowly, but that's what we do with allopurinol for any patient." High blood levels of oxypurinol that can occur in patients with renal impairment must be avoided because they boost the risk of a hypersensitivity reaction, milder allergic reactions, or other forms of intolerance. Dr. Simkin said he had no disclosures

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relevant to febuxostat and allopurinol.

Other specialists say that now that febuxostat is an option, they'll avoid potential problems by immediately jumping to the new drug for patients with impaired renal function. "Allopurinol should be first-line therapy in treating patients with hyperuricemia and gout unless their renal function prohibits use of allopurinol," said Dr. Robin K. Dore, a rheumatologist at the University of California, Los Angeles. Dr. Dore said she has been a consultant to and has been on the speakers bureau of Takeda, and she participated in some febuxostat studies.

The strategy of avoiding allopurinol entirely in patients with renal dysfunction and going straight to febuxostat was also endorsed by Dr. Naomi Schlesinger, a rheumatologist at the University of Medicine and Dentistry of New Jersey, in New Brunswick. Dr. Schlesinger said that she has served on an advisory board and the speakers bureau of Takeda, and that she has also received research funds from the company.

But febuxostat should not be considered completely free from renal concerns, said Dr. Ted R. Mikuls, a rheumatologist at the University of Nebraska in

Omaha. "Studies of febuxostat have not included patients with a serum creatinine level of more than 2.0 mg/dL that I'm aware of," he said in an interview. "The medical community must demand a lot more data before using [febuxostat] widely in patients with renal failure." In addition, "I'm not aware of data that allopurinol damages kidneys. What most rheumatologists do is dose it very judiciously in patients with renal dysfunction, gradually increasing it to get the uric acid level where it needs to be." Dr. Mikuls said he had no disclosures relevant to febuxostat and allopurinol.

A small percentage of gout patients (often estimated at fewer than 10%) are intolerant of allopurinol. Intolerance can range from a serious hypersensitivity reaction to a milder allergic reaction or another form of adverse reaction, such as gastrointestinal distress. A patient with hypersensitivity to allopurinol is someone for whom "febuxostat could be really helpful," but this is "pretty rare, far less than a few percent," Dr. Mikuls said.

For treatment of symptomatic gout, the guiding number to look at is the serum level of uric acid. When the level drops below 6.0 mg/dL, existing uric acid crystals disappear by dissolving into the blood, thereby alleviating symptoms.

Although many patients respond to an allopurinol dosage of less than or up to



**It's a reasonable strategy for patients with renal dysfunction to go straight to febuxostat.**

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300 mg/day (especially if they have renal dysfunction such that their blood level of oxypurinol is unusually high relative to their allopurinol dose), the majority of patients needs more than 300 mg/day, Dr. Simkin said. "It's appropriate to use up to 800 mg/day," and dosages of 300-800 mg/day are usually effective, he added. But doses this high are also not often prescribed by physicians. "The main reason [why patients have uncontrolled gout] is misuse of allopurinol. Patients don't get treated with adequate doses."

Patients who don't respond to high allopurinol doses are "very rare," Dr. Simkin noted.

When patients don't respond adequately to 300 mg/day of allopurinol, Dr. Mikuls pushes the dosage as high as 800 mg/day, although he's not comfortable treating patients at this level. Patients who are still not at the serum uric acid goal at 800 mg/day should be switched to febuxostat, although it remains unclear how these patients respond following the switch. "I think we'd all like to see a data-driven answer to that question," he said.

"Every study of the quality of gout care suggests that patients get suboptimal care, including suboptimal use of urate-lowering treatments. If febuxostat serves any purpose, it's to highlight the condition and what is appropriate care," Dr. Mikuls said.

What does all this mean for the number of gout patients who should get febuxostat? Estimates on the low end range down to fewer than 5%, according to Dr. Simkin, whose total is mostly patients who are intolerant of allopurinol, with just a few added who don't respond to a dosage as high as 800 mg/day. On the high end, Dr. Schlesinger estimated that "millions" of U.S. gout patients need febuxostat. She included in her estimate all gout patients with chronic kidney disease, those who don't respond to a 300-mg/day allopurinol dosage, and those who are allopurinol intolerant. ■

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