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by Lynne Peterson

Quick Pulse

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Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com
TrendsInMedicine@aol.com

FDA Advisory Committee Recommends Approval of New Gout Drug – But with Restricted Access

Silver Spring, MD
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The FDA's Arthritis Advisory Committee voted 14 to 1 to recommend approval of Savient's Krystexxa (pegloticase) – formerly known as Puricase – a recombinant pegylated form of the porcine uricase enzyme for treatment-failure gout. However, the panel clearly wanted the drug limited to severe patients who had failed allopurinol or Takeda's Adenuric (febuxostat) under a Risk Evaluation and Mitigation Strategy (REMS).

Pegloticase was granted orphan drug status in 2001, and Savient tested it under a Special Protocol Assessment (SPA) with the FDA. The company is seeking approval for 8 mg/dL infusions every two weeks for:

> Patients with treatment-failure gout to control hyperuricemia and to control or improve the signs and symptoms of gout including: reduction of tophus burden, reduction of chronic pain, improvement of physical functioning, and decreased frequency of gout flares.

The PDUFA date is August 1, 2009, but since the details of the REMS need to be worked out, it is likely that final FDA approval will be later than that. Thus, the Agency may issue a Complete Response letter on or before that date, leaving the details of the REMS to be worked out.

The advisory committee was composed of 15 voting members – 8 rheumatologists, 3 cardiologists, a consumer representative, a statistician, a toxicologist, and an NIH (National Institutes of Health) official. Dr. Jeffrey Siegel, clinical team leader in the FDA's Division of Anesthesia, Analgesia, and Rheumatology Products, Center for Drug Evaluation and Research (CDER), opened the meeting by stating: "The FDA does not contest the sponsor's view of the efficacy of pegloticase…We are focusing the bulk of our presentation on the safety issues that have come up. These safety issues focus on several areas. We observed a higher rate of cardiovascular (CV) serious adverse events with pegloticase patients vs. controls. In addition, pegloticase is immunogenic – giving the product causes antibodies to develop. There is a higher rate of infusion reactions with pegloticase, and we will discuss that and possible cases of anaphylaxis."

The FDA Perspective

Efficacy is not an issue. FDA officials said the Agency "does not dispute the efficacy" of pegloticase. The FDA reviewers concluded that both doses of pegloticase tested in Phase III – 8 mg/dL every two weeks (Q2W) or every four weeks (Q4W) – normalized plasma uric acid (PUA) in significantly more patients than

placebo. A reviewer wrote, "In addition to lower plasma urate levels, patients treated with pegloticase had a significant reduction in tophi (for those with at least one tophus at baseline), reduction in swollen and tender joints, and a decrease in the frequency and severity occurrence of gout flares among patients who received pegloticase every 2 weeks as compared to placebo." However, some of the secondary assessments only trended toward improvement (p=Nss) in the pooled analyses of patients who received pegloticase every four weeks.

Rather, the issue for the panel was safety, particularly CV events, infusion/allergic reactions, and antibodies. The FDA reviewers noted that the Agency generally requires a safety database of 1,500 patients treated overall, 300-600 treated for ≥6 months, and 100 treated for ≥1 year, but smaller numbers are acceptable because this has been designated an orphan drug.

➢ **Serious cardiovascular events**, though the Agency noted that most of the patients developing these problems had other CV risk factors and that the numbers were small, causing "uncertainty" as to whether there is a genuine safety signal. FDA reviewers said that there is evidence linking hyperuricemia to gout as well and evidence that patients with hyperuricemia have a greater risk of CV disease, and they offered two hypotheses for this:

1. That patients with hyperuricemia often have other risk factors for cardiovascular disease.
2. That hyperuricemia by itself predisposes to CV risk.

The FDA's internal CV consultant concluded:

- The CV serious adverse events occurred in patients with pre-existing comorbid risk factors for major cardiac adverse events.
- Occurrence of these events is not unexpected in view of the high prevalence of underlying CV disease in the patient population in the trials.
- There are too few cardiac serious adverse events to allow detection of any pattern in their occurrence, resulting in ***a degree of uncertainty about the cardiac safety of pegloticase***.

➢ **Infusion reactions and allergic reactions**.

- **Infusion reactions.** The FDA said these peaked at Dose 3 (44%) for Q4W and at Dose 4 (23%) for Q2W. Reactions were managed with supportive medical care and monitoring and slowing/stopping the infusion, and administration of IV fluids, diphenhydramine and/or corticosteroids. The most common sign/symptoms were urticaria (11%), chest discomfort/pain (10%), erythema (10%), pruritis (10%), dyspnea (7%), and flushing (6%).
- **Hypersensitivity reactions.** The FDA said many of the infusion reactions had features of allergic reactions, and some had characteristics of anaphylaxis. The FDA's allergy consultant concluded that the estimated frequency of anaphylaxis with pegloticase is 5.1% (7.3% with Q2W and 3.9% with Q4W), "However, these frequencies would likely have been higher but for the mandatory prophylaxis regimen employed in the Phase III studies to prevent infusion reactions."
- There were no deaths from infusion reactions or allergy reactions. In most cases, patients meeting the criteria for anaphylaxis with pegloticase had treatment discontinued, but five patients received additional infusions of pegloticase, and three of these had no additional reactions.

➢ **Antibodies** leading to adverse effects on safety and efficacy. The FDA found that patients who had moderate-to-high levels of anti-pegloticase antibodies, had substantially higher rates of infusion reactions.

The FDA reviewers concluded:

- Pegloticase Q2W resulted in statistically significant improvement in both PUA and clinical responses, but a decrease in efficacy was associated with increasing levels of anti-pegloticase antibodies.
- The rate of death was higher with pegloticase Q2W (4%) vs. Q4W (1%) or placebo (2%). The deaths were due to infections and CV events and occurred in patients with multiple underlying risk factors.
- A higher rate of serious CV events was observed with both dosing regimens of pegloticase. No dose response or pattern for these events was observed, and they occurred in patients with multiple risk factors for these events.
- Serious infusion reactions were more frequent with pegloticase Q2W vs. placebo (26% vs. 5%), and 5% of patients met the criteria for anaphylaxis.
- Pegloticase is highly immunogenic, with seroconversion rates of 88% with Q2W dosing and 89% with Q4W dosing.

THE COMPANY PERSPECTIVE

Steven Hamburger, PhD, group vice president for Quality and Regulatory Affairs at Savient Pharmaceuticals – introduced the company speakers. Dr. Michael Becker from the University of Chicago Pritzker School of Medicine outlined the need for a drug like pegloticase. He said treatment-failure gout (TFG) is an unmet medical need, affecting ~50,000 patients. But he also noted that patients with TFG have a high incidence of comorbid CV and metabolic disorders that complicate gout therapy and increase the underlying risk for disability and death.

In the U.S., Dr. Becker estimated that there are 15-20 million people with asymptomatic hyperuricemia, and 20%-30% will

progress to gout. About 4-5 million Americans have gout flares, with urate lowering indicated in 3-4 million. Of those, 200,000-400,000 have poor urate control and progressive symptoms, and 40,000-60,000 develop treatment-failure gout.

The mainstay of gout therapy has been allopurinol, but many gout patients do not reach the serum urate goal on the U.S. dose of ≤300 mg/day. He said it takes months to years for allopurinol therapy to show clinical benefits, and the factors contributing to low dosing of allopurinol include: intolerance (with rare but life-threatening rashes and hypersensitivity syndrome), dosage reductions in patients with renal impairment, and "minimal" evidence of safety and efficacy for higher doses.

Dr. Vibeke Strand, a rheumatologist from Stanford University, reviewed the efficacy of pegloticase. She said transient responders can be identified by routine SUA (serum uric acid) monitoring, usually with the first 3 months of therapy. With Q2W dosing, the majority of persistent responders maintained responses through Week 53.

Dr. Strand estimated the number needed to treat (NNT) with pegloticase based on patient reported outcomes:

- 1.2 for an improvement in ≥1 of 4 parameters.
- 1.6 for an improvement in ≥2 of 4 parameters.
- 2.4 for an improvement in ≥3 of 4 parameters.
- 4.5 for an improvement in all 4 parameters.

Results of Phase III Trials of Pegloticase

Measurement	Placebo n=43	Pegloticase Q2W n=85	Pegloticase Q4W n=84
Baseline			
Allopurinol contraindicated	87% - 90%	69% - 93%	77% - 83%
Allopurinol ineffective	10% - 13%	7% - 31%	17% - 23%
Tophi present	65% - 70%	67% - 79%	76% - 77%
≥1 CV condition/risk factor	81%	85%	85%
Efficacy			
Primary endpoint #1: PUA responders in CO405 trial	0	47% **(p<0.001)**	20% **(p=0.044)**
Primary endpoint #2: PUA responders in CO406 trial	0	38% **(p<0.001)**	49% **(p<0.001)**
Secondary endpoints **(pre-specified pooled analysis)**			
Complete tophus response	7%	40% **(p=0.002)**	21% (Nss, p=0.20)
Gout flares in Months 4-6	67%	41% **(p=0.007)**	57% (Nss, p=0.321)
Tender joint count	-1.2	-7.4 **(p=0.008)**	-6.1 **(p=0.024)**
Physician Global Assessment of disease activity	-8.2	-28.2 **(p<0.001)**	-23.6 **(p=0.003)**
Patient Global Assessment of disease activity	+0.83	-11.85 **(p=0.02)**	-12.64 **(p=0.011)**
Patient reported pain	+1.37	-11.45 **(p=0.040)**	-6.91 (Nss, p=0.124)
HAQ-DI	+0.02	-0.22 **(p=0.026)**	-0.20 **(p=0.025)**
SF-36	-0.3	+4.38 **(p<0.001)**	+4.94 **(p<0.001)**

Dr. William Schwieterman, a well-respected former FDA official in the Center for Biologics Evaluation and Research (CBER) who is now an independent consultant, presented the company's view of the safety of pegloticase. He said, "In our opinion, the risk:benefit for this drug is extremely positive. The treatment-failure gout population presently has no available therapy. This is the first and only drug to show resolution of tophi. The risk is predictable and manageable. Stopping therapy when SUA is >6 mg/dL (transient responders) will eliminate infusion reactions in 91% of patients, eliminate injection reactions suggestive of hypersensitivity in 82% of patients, and reduced drug exposure in transient responders not likely to benefit from therapy."

In Phase III:

- 140 patients were exposed to pegloticase ≥6 months.
- 121 patients for ≥12 months.
- 95 patients for ≥18 months.

Safety in Phase III Trials of Pegloticase

Measurement	Placebo n=43	Pegloticase Q2W n=85	Pegloticase Q4W n=84
Discontinuations			
Any reason	9%	31%	30%
Adverse events	2%	21%	21%
Infusion reactions	0	11%	13%
Gout flares	2%	5%	2%
Deaths	3 patients *	3 patients	1 patient
Other safety data			
Serious adverse events	12%	23%	23%
Infusion reactions	5%	26%	40%
Infusion reactions reported as serious adverse events	0	5%	8%
Gout flares	81%	77%	83%
Serious gout flares	5%	5%	1%

*** Deaths were not censored for the analysis.**

Dr. William White, a cardiologist from the University of Connecticut School of Medicine, reviewed the CV safety of pegloticase. He emphasized that there is a high prevalence of CV disease and CV risk factors in treatment-failure gout patients.

Dr. White concluded:

- Patients in the pegloticase trials had a high risk for CV events, reflective of a population with treatment-failure gout.
- Clinical data showed no changes in major CV risk factors with pegloticase relative to placebo.
- There was no increase in CV event rates over time with up to 16 months of treatment.

- APTC (Antiplatelet Trialists' Collaboration) events – a standardized way of measuring CV safety – were low in number and occurred in 3/169 pegloticase patients vs. 0/43 placebo patients.
- All-cause mortality occurred in 4/169 pegloticase patients and 3/43 placebo patients. An additional death occurred in a placebo patient that was randomized but not dosed.
- APTC events occurred in patients with ≥4 CV risk factors. High titer antibodies were ***not*** associated with CV events.

Cardiac Safety in Phase III Trials of Pegloticase

Measurement	Placebo	Pegloticase	
		Q2W	Q4W
	n=43	n=85	n=84
Adjudicated APTC CV events			
All APTC	0	2.4%	1.2%
CV death	0	2.4%	0
Non-fatal MI	0	0	1.2%
Non-CV deaths	7.0%	1.2%	1.2%
Adjudicated non-APTC CV treatment-emergent events			
All non-APTC CV events	0	2.4%	7.1%
Non-fatal CHF	0	2.4%	1.2%
Arrhythmia	0	1.2%	1.2%
CV events by CV risk factors/disease			
APTC events with 0-3 CV risk factors	0	2.6%	0
APTC events with ≥4 CV risk factors	0	11.1%	7.7%
CV events by anti-pegloticase antibody level			
APTC events with high titer	0	2.6%	0
APTC events without high titer	0	2.2%	2.2%
Non-APTC events with high titer	0	0	8.1%
Non-APTC events without high titer	0	4.4%	6.7%

Savient has proposed a risk management plan, but the panel clearly didn't think this was sufficient. Dr. Schwieterman outlined the key features of the company's plan:

- A two-year, 3,000-patient post-approval registry – with an independent data safety monitoring board – to collect and monitor additional safety data, including CV events.
- Ensuring that pegloticase is used only in patients with treatment-failure gout.
- Facilitating informed benefit:risk decision-making.
- Education on label recommended prophylaxis to minimize the risk of infusion reactions and gout flares.
- Education regarding dose/schedule, routine monitoring of serum uric acid, and the appropriate discontinuation of therapy in patients with a rising SUA.

Dr. Becker summed up by saying, "Pegloticase 8 mg Q2W IV in treatment-failure gout patients results in prompt and dramatic clinical improvements and disease modification, has an acceptable safety profile in light of the debilitating disease, and provides an effective therapy in this orphan sub-population of gout patients…The risk associated with pegloticase Q2W…is predictable and manageable. Increased incident of gout flare is transient. Infusion reactions can be avoided by stopping treatment in patients with loss of serum urate response. Exposure in transient responders is minimized with serum urate monitoring. Any possible CV risk is addressed with the comprehensive risk minimization plan."

Panel Questions for Company and FDA Experts

Questions for Savient officials and experts

During questioning by panel member Dr. Curt Furberg, a cardiologist from Wake Forest University, Savient sources indicated the company is seeking approval for a 12-month course of pegloticase therapy, not lifelong treatment.

- Dr. Furberg commented, "You are proposing lifelong treatment, and you only have 6-month data. That is my concern…I am impressed by the acute data – the 6-month efficacy data, with resolution of urate deposits, etc. But after all the tophi are gone and you remove the deposits, do you still need to give the same dose (8 mg Q2W)? In my view the maintenance dose could be possibly lower. I think this is an issue that is both clinical and relates to cost-effectiveness."
- Savient expert Dr. Schwieterman said, "We agree this is an important issue. We are not actually proposing treatment for life…Optimal treatment duration with pegloticase has not been established…The 120-day safety update shows continuation of these benefits, so we are going to discuss this with the Agency, but our recommendation at this point is a 12-month recommendation, guided by the physician, the patient, and the patient response…and then maintenance therapy with some other agent."
- Savient expert Dr. Strand said, "Seventy-one percent of ITT (intent-to-treat) patients were followed 18 months. That is 60% of the active treatment group and quite a few of the placebo patients. We can show that not only is there maintained response but further resolution of tophi, and patients continue to have improvement in other parameters…If you look at the folks who got Q2W and then went to Q4W in the open-label extension, their responses continued, but they were not as good in the first six months and were not as well maintained in the open-label extension."
- Savient expert Dr. White added, "I see no reason that febuxostat could not be used after a course of pegloticase therapy."

Cardiologist Dr. Milton Packer of the University of Texas Southwestern Medical Center spent a long time questioning company officials about the usefulness of SUA >6 as a cutoff. The chair finally cut the discussion off with no real resolution of the issue.

Questions for the FDA

The key questions for FDA officials dealt with blinding, statistical analysis, risk:benefit, anaphylaxis, the patient population, the proposed post-marketing registry, dosing regimen, the safety database size, and predictors of response. Interestingly, Dr. Siegel chose to answer many of the questions rather than the FDA reviewer, which is somewhat unusual.

Statistics. For the primary endpoint, dropouts were considered by the FDA as non-responders. For the secondary endpoints, a last observation carried forward (LOCF) method was used. Dr. Packer asked if the secondary endpoint results would have been worse if the same statistical approach was used as for the primary endpoint, and an FDA statistician said yes, that was a fair assessment.

Risk:benefit. Dr. Lenore Buckley, a rheumatologist from Virginia Commonwealth University School of Medicine, estimated that 40%-50% of patients getting pegloticase will respond to the drug, but everyone taking it has a 30% risk of a serious adverse event, and the FDA reviewer agreed with those assumptions.

Anaphylaxis. The industry representative on the panel, D. Bruce Burlington, a pharmaceutical consultant, asked about the FDA's choice of anaphylaxis definition. An FDA allergy and pulmonary expert said, "Anaphylaxis is inherently unpredictable…and potentially life-threatening. It is reassuring that in this pegloticase database there were no fatal events, but we can't be reassured that it won't occur in the future. I think it is a risk that needs to be acknowledged."

Patient population. Dr. Michael Weisman, a rheumatologist from Cedars-Sinai Medical Center in Los Angeles, wondered if febuxostat will make an impact on the natural history of gout and diminish the pool of patients eligible for pegloticase. Dr. Rosemarie Neuner, a clinical reviewer in the FDA's Division of Anesthesia, Analgesia, and Rheumatology Products, responded, "That is a very good question…When we gave this priority status, it was based at that time on an unmet medical need because febuxostat was not approved. Now that it is approved, there are other options…but that doesn't mean this product doesn't have additional efficacy, such as patients with (tophi)…The treatment of tophaceous disease is time consuming. You have to be very, very patient. I don't ever remember in 20 years of practice seeing a tophi disappear… even if the allopurinol dose is increased to maximum tolerable levels...Time will tell (with pegloticase). It will depend on practice preferences, and how people will utilize these various products. It is too soon to make judgments or calls."

Registry. The company is proposing a registry and a panel member wanted to know if it would be mandatory or voluntary. Dr. Siegel didn't answer that question, but he said it could be designed either way – voluntary or mandatory as with Biogen Idec/Elan's Tysabri (natalizumab).

Choice of dose. Dr. Sanjay Kaul, a cardiologist from Cedars-Sinai Heart Institute in Los Angeles, was curious about differences in the efficacy results in the two Phase III trials. Dr. Siegel responded, "It is unexpected…We would have expected similar results." Dr. Siegel offered two possible explanations: variability in response or a statistical quirk.

Dr. Kaul also noted that the Q4W dosing regimen has a more desirable adverse event profile, with about half the rate of anaphylaxis and fewer deaths than the Q2W regimen. The FDA's Dr. Neuner responded that the Q4W regimen did not have tophus resolution, "Even though Q4W captured the primary endpoint, it didn't capture tophi as clinically important." Dr. Siegel added, "The sponsor proposed Q2W; that is their preference. We are interested in what the committee thinks of the two dosing regimens…Clearly, with respect to tophi, it was higher resolution with the Q2W regimen. The rate of infusion reactions was higher with Q4W, but we are definitely open to comments for consideration of other doses."

Safety database size. Robert Stine, PhD, a statistician from Wharton, expressed concern about the small size of the safety database (85 patients). Dr. Siegel explained that this is an orphan indication, so a small database for safety may be acceptable, but he is looking for guidance from the panel on whether there are enough data.

Predictors of response. Dr. Stine wondered if there were any genomic (or other) markers to predict responders, but Dr. Curtis Rosebraugh, director of the FDA's Office of Drug Evaluation II, CDER, said that, unfortunately, there are no tests yet that can predict responders.

PUBLIC SPEAKERS

Patients made heartfelt pleas for access to pegloticase, telling how it had changed their lives. FDA officials and panel members were clearly impressed with the stories.

Dr. Herbert Baraf, a rheumatologist from George Washington University and a clinical investigator for pegloticase. "My experiences with the pegloticase program were extraordinary…Our site enrolled six patients in Phase II, including a 67-year-old oncologist, Dr. S., who was our first patient…I was astounded to see that his tophi resolved. Tophi do not resolve in three months, not even in three years with standard treatments." He also saw similar results with another patient.

Dr. Baraf has 13 patients in the Phase III trial. He described two patients who were allergic to allopurinol and had large tophi deposits. He said that in less than 12 weeks her foot ulcers healed, and in 6 months her tophi resolved. Another

patient who was initially in the placebo group but changed to pegloticase during the open-label period and was able to walk.

He said, "I don't remember participating in any trial where patients were so profoundly affected by a treatment. I appeal to the committee to support access to pegloticase…Pegloticase is a powerfully effective therapy."

Barney Rush, CEO of H2Gen Innovations. He described how his father suffered from gout, with severe, painful, disabling tophi on his hand and elbow. After a few weeks in the pegloticase trial there were "remarkable" results without any serious adverse events.

Bethel Dinwiddie, a gout patient who took pegloticase. "Without it, I can definitely say I wouldn't be here. I had given up on everything about life. I had retired, couldn't walk, and everything I did I had to depend on someone else to help me with. The fire department had to get me out of bed and put me in a car, and, of course, take me back out of the car and put me back in the bed when I got home…In a situation like that your friends and relatives soon get tired of doing it, so I decided life wasn't worth living. But I was fortunate to have a doctor who introduced me to this (pegloticase) program." After pegloticase he was able to come to this meeting!

Timothy Schwarz, a gout sufferer and single father of two. "I thought I was the worst case of gout until the cases I saw (here). I haven't had the chance to have the (pegloticase treatment)…If I work more than 2 hours, I flare up and am down, crippled for a week…The pain I can't exaggerate enough…(Pegloticase) will give me hope and an opportunity to live again."

Lonnie Mathews, a gout patient whose hotel was paid by Savient and who owns Savient stock. "The gout I controlled with allopurinol for 30 years until my kidney failure worsened. In 5 days, I was suffering a gout attack more severe than any I ever had…Gout attacked my hands, feet, toes…I suffered for about 1 year, until (I got in the pegloticase trial)…I could not walk, was confined to bed or a wheelchair…My uric acid was 22. About six months after the treatment I suffered a heart attack…In my opinion, it was not related to the drug…Pegloticase has changed my outlook on life and made it worth living again, despite all the medical problems…Since I got my last pegloticase, I have had no gout flares but I am incredibly fearful about not having access to this drug."

Jeraldene White, a gout patient with tophi who received travel assistance from Savient. She said, "There was really nothing that could be done, and it was distressing. Then, I found out about the pegloticase clinical trial…When I received my first dose, I couldn't move any of my fingers, joints, or stand…but after my first pegloticase dose I began to notice slight changes in the movement of my fingers…This improvement in mobility continued during the course of the trial, and today I am able to lead an active life, and all of the mobility has been restored to my joints."

Ernest Legg, a gout patient. He was first diagnosed in 1993, and started on allopurinol, but had severe side effects to it that required stopping the drug. His gout progressed, and his condition worsened, with tophi buildup, "I was basically becoming crippled…I started on pegloticase and the fact that I walked to this microphone is a miracle of modern medicine. The tophi are gone, I regained the use of my hands, I got a motorcycle. Life is on the upswing. Please, please, please consider approving this drug. It has helped me regain my life, and I'm sure there are millions of other people who could benefit, too."

PANEL CONSIDERATION OF FDA QUESTIONS

Question 1. Discuss whether the data generated by the Phase III trials suggest that pegloticase increases CV risk.

The panel chair, Dr. Kathleen O'Neil, a pediatric rheumatologist from the University of Oklahoma College of Medicine, summarized the panel comments: "Most do not find the evidence overwhelming, and certainly the statistics don't tell us that is the case, that this drug causes CV risk, but we all seem to share a concern that the drug will be used in a population with high baseline CV risk…What we might and might not gain from a registry, I don't think any of us are convinced that would work."

Panel comments included:

- *Dr. Tuhina Neogi, a rheumatologist from Boston University School of Medicine:* "We should expect some level of events, and with so few in the placebo arm, it is very difficult to tell if it is an expected or higher-than-expected rate."
- *Dr. Daniel Clegg, a rheumatologist from the University of Utah School of Medicine:* "The numbers are small, and we would expect to see some incidence of events…The playing field has changed since these (pegloticase) studies were redeveloped…I'm interested in **how strict a registry can be developed**. If we could develop a mandatory registry that would compel uric acid measurement before this agent is considered, I think this agent has the potential to improve lives that otherwise can't be addressed with current therapy."
- *Diane Aronson, the consumer representative:* "I am impressed with the patient testimony."
- *Dr. Stine, the statistician:* "I already expressed my concern on the sample size…especially in the absence of any (identified) mechanism…I think this is a very difficult issue to resolve, and we have to use judgment because the statistical evidence is going to be uncertain."

- *Dr. Buckley, a rheumatologist:* "I think the sample size is inadequate to answer (the CV risk question)."
- *Dr. Ted Mikuls, a rheumatologist from the University of Nebraska Medical Center:* "Clearly, the sample size is an issue. I don't think anyone would argue with that…You could potentially have more cardiac problems because of efficacy…I would propose if a safety registry comes together, that we look at that (efficacy associated with more cardiac problems)…(And) are there associations with bolus steroids, with increasing NSAID use?...This is a very, very vulnerable patient population."
- *Panel chair:* "(There is a) known CV risk of NSAIDs – and I do suspect a lot of people are using over-the-counter NSAIDs and perhaps forgetting to enter them (in their patient history). That may be sufficient to double their risk, which is already quite high for a thrombolic event… Because of the limits of the size of the population this drug is targeted for…and the high risk factors, it is going to be very hard *a priori* to get the data we need."
- *Dr. Nancy Olsen, a rheumatologist from the University of Texas Southwestern Medical School:* "I'm not convinced there is an increase in CV risk…There is a risk of infusion reactions…The other thing that struck me was that there are so many heart problems that were reported that it is difficult to find a unifying mechanism."
- *Dr. Lewis Nelson, an emergency room/toxicologist from New York University School of Medicine:* "I have mixed feelings…On the one hand, it is pretty clear there is a signal, a somewhat disparate (CV) signal…On the other hand, there is the biological plausibility issue…A mechanism would be nice…Maybe there is a chicken and egg thing here…but I do think that the numbers are there. They are small numbers…but it is something we must look at and try to figure out…The other thing that troubles me is that we are looking at this not necessarily in a real-world environment…When this gets out, I think all bets are off, so we should have a pretty good handle on the real risk when it gets out."
- *Dr. Furberg, a cardiologist:* "I find the CV data inconclusive…I think we need a better designed registry with a truly independent oversight committee, not a sponsor-supported oversight committee."
- *Dr. Weisman, a rheumatologist:* "I think it could have been foreseen when the orphan drug status was applied that the numbers would be small in a population where the CV rate would be high. So, what do we do?...The answer, I think, is that this requires a **mandatory safety registry** for all patients going on this drug."
- *Dr. H. James Williams, a rheumatologist from the University of Utah:* "I do think we need further monitoring, and I think a **registry** would meet that need."
- *Dr. Packer:* "I'm scratching my head because so many people say you can't interpret the CV side effect profile without a mechanism…Most mechanisms for both efficacy and safety are fabricated…We make them up after the fact and after we know there is, in fact, an effect, either a beneficial or detrimental one...Although we all would love to know what the mechanism is, if someone proposed it, you wouldn't be any smarter…I have no way of interpreting the (CV event) imbalance. Is there an imbalance? Yes. Does it mean anything? I don't know how anyone would know. The thing that is sad is that I don't think a registry will answer that question because these patients have enormous CV risk factors…Would I propose a registry? No. I don't think that, after five years of entering patients in a registry, we will know any more about the CV profile of this drug."
- *Dr. Kaul:* "I think the sponsor made a compelling argument that there is a unmet need, and the efficacy is indisputable…In such situations I try to find a way to minimize exposure to risk. How to do that? Restrict access…One way to do that is to redefine what treatment-failure gout means…Perhaps only offer this to patients who failed febuxostat…The only way we can minimize exposure is to restrict the patient population."

Question 2. Discuss the efficacy, safety, and overall clinical utility of pegloticase in the treatment of refractory chronic gout.

Panel member comments included:

- *Dr. Weisman, rheumatologist:* "The data are adequate to show clinical utility, and the infusion reactions can be managed."
- *Dr. Williams, rheumatologist:* "I think safety has been clearly demonstrated…I think it would be used in patients who didn't respond to either allopurinol or febuxostat but also in patients with tophi…I can see short-term use of this drug, then going on to controlling their gout (with febuxostat or allopurinol)…We have other drugs that cause infusion reactions, and we are aware of those, and that can be dealt with…I don't want to imply that every tophi should be treated with this drug…I think the large tophi, this would be (good)…And the definition of treatment-refractory gout is wide enough that I could use it for whatever I want."
- *Dr. Packer, cardiologist:* "It is important to try to understand that this is the first drug to ever show complete resolution of tophi. The sponsor should get credit for that in the (label), and that should be used to define the appropriate population…I am concerned about what the sponsor is proposing as a cutoff for uric acid between responders and non-responders."
- *Dr. Kaul, cardiologist:* "The overall efficacy has been established convincingly…but there are lingering questions about dosing strategies…On safety, I still maintain the most effective strategy to mitigate risk is to **minimize**

the patient population that will be exposed…I think we should try (other therapies) before arriving at this very efficacious therapy."

- *Dr. Douglas Rosing, NIH:* "I think this is efficacious in their well-described population…My concern is when the drug is released, the inclusion and exclusion (criteria) may not be followed closely, and that is where we could get into problems."
- *Industry rep:* "It seems to work well…Further evidence of efficacy is that after the first couple of months, flares go down as well…It is clinically efficacious in carefully selected patients."
- *Dr. Neogi, rheumatologist:* "Q2W had greater efficacy than Q4W…but SUA goes very low, than any other treatment we've seen, and there can be some potential long-term effects from that…There is some evidence that very low uric acid has a negative impact on neurological status…so, CV events are not the only issue to watch…If someone can't take febuxostat for maintenance, what happens then?…We need more information on what happens after stopping pegloticase and redevelopment of gout…Most rheumatologists have dealt with infusion reactions, and the sponsor's plan seems reasonable for potentially identifying individuals. Eventually, I think we will have other markers for antibody increase…The definition of treatment-failure gout is now going to change with the availability of febuxostat, so we may see a smaller and smaller patient population for which this drug will be of value…but even if it is smaller, they need this drug."
- *Dr. Clegg, rheumatologist:* "I share the safety concerns …I'm not as pessimistic about other agents to develop hyperurecemia…I think we can educate our colleagues about optimizing those therapies to limit the population that would need exposure (to pegloticase)."
- *Consumer rep:* "What happens after patients stop (pegloticase)?...Another concern I have relates to the deaths."
- *Dr. Buckley, rheumatologist:* "This is a very effective drug for short-term control…I think the safety can be improved by choosing the patients or stopping treatment. I'm concerned about this drug…This is a chronic disease, and it is unclear what the role of this drug will be…I think this drug may go into much wider use than we think it will be, and rheumatologists or nephrologists will have their own idea of what they think is the best treatment… By trying to define treatment-failure gout, we think we can control use, but…we have to be prepared for this not to be used in a (limited way)…This may have a much broader market…I think long-term use needs to be more carefully thought out, and we may not be able to control the patient population."
- *Dr. Stine, statistician:* "I agree the drug has been shown to be highly efficacious…though there is a concern that it is too good to be true…We all agree there are questions about safety but not issues we can resolve here…As the genie gets out of the bottle, and we see much wider use – the word will be out that there is a miracle thing – there will be demand for patients who don't meet this protocol …How you try to watch that I'm not sure. I'm not sure (labeling) is enough."
- *Dr. Mikuls:* "I do think there is a need for this…Is the drug efficacious? It certainly appears to be…We haven't talked a lot about resolution of tophi previously…On CV risk, we discussed that…and maybe surveillance is needed there…The infusion reactions, which I believe are mitigated by the sponsor's plan, at least in part...I am very concerned about the suboptimal care that is out there. And I am concerned this drug will be used in patients it is not appropriate for."
- *Chair:* "The sponsor has nicely documented efficacy for lowering uric acid and controlling a number of the consequences of hyperurecemia…The question of efficacy is not a big question at this point…On how to assure the drug is used appropriately, unfortunately, there isn't a whole lot of ways to do that…Third party payers will not allow this drug – will not be as inexpensive as allopurinol – to be used unless there is demonstration of a certain number of criteria…and I'm sure it will have to be prescribed by a physician with some expertise in gout and prescribed at first to a patient who has failed (another therapy) to the insurance company's satisfaction."
- *Dr. Olsen, rheumatologist:* "I'm less concerned about safety…because in the appropriate population, the benefits outweigh the risks…It would be nice to have materials to educate patients about gout."
- *Dr. Nelson, toxicologist:* "I do think the efficacy itself is clear. The safety is questionable…The overall clinical value, I think becomes a risk:benefit analysis, and we are missing one part of the question…I think more information is needed."
- *Dr. Furberg, cardiologist:* "I'm okay on efficacy…On safety, it depends. I'm unwilling to sign a blank check. I'm leaning to **conditional approval**, with approval depending on the wording of the labeling, particularly the sections on contraindications, precautions, warnings, etc. Approval also should depend on the MedGuide. I like that…Approval also should depend on what we decide about additional studies, the post-marketing studies… And, finally, the main worry is long-term safety. Since we don't know the mechanism of action…how can we say with six-month data that this drug is safe?…We need much more information on the long-term effects."

The FDA's Dr. Rappaport made a statement that appeared to reassure the panel: "I want to be sure people understand our authority now…We now have the authority to mandate certain safety interventions and risk management strategies, including mandating studies in the post-marketing period. We can now require them, and it is an enforceable requirement…We can

also mandate a REMS, and a REMS could include a number of different features – a MedGuide or also things like we could actually implement a prescriber registry, a dispenser registry, and a patient registry – any or all of those as deemed appropriate for the drug in question, to restrict its use to the appropriate population. The onus then falls on the sponsor to ensure whatever the restrictions are actually occurring and people are not receiving off-label drug…These new authorities do have teeth."

Question 3. In view of the data submitted for safety and efficacy, do you recommend approval of pegloticase for the treatment of refractory chronic gout?

VOTE: 14 Yes, 1 No

The one negative vote came from the consumer representative, who explained, "There weren't enough data…I felt (we needed) more periodic information on blood pressure and EKGs, and liver enzymes – given the acetaminophen load."

Other panel member comments included:

- *Dr. Buckley, rheumatologist:* "I would vote for limited use given the lack of long-term safety data."
- *Dr. Stine, statistician:* "Discussions of REMS and subsequent strategies are important."
- *Dr. Mikuls, rheumatologist:* "There is an unmet need and a very needy patient population."
- *Chair, rheumatologist:* "Yes, because of the unmet need, the fairly impressive efficacy, and the ability to try to put some limits on the use of this drug."
- *Dr. Olsen, rheumatologist:* "I do think this drug would fulfill an unmet need."
- *Dr. Nelson, toxicologist:* "Yes, with the assumption that, at a minimum, we go with the REMS recommended by the company."
- *Dr. Furberg, cardiologist:* "We are assured that you (the FDA) will restrict use to the appropriate population."
- *Dr. Weisman, rheumatologist:* "Yes, because of the impressive efficacy for what was the orphan drug status and (for) the ability of the FDA to step up and do what we just heard they are able to do (a tough REMS)."
- *Dr. Williams, rheumatologist:* "Yes, because of the demonstrated efficacy and because there is a need for the drug."
- *Dr. Packer, cardiologist:* "The effects of this drug are so striking that they could be demonstrated on a small population…We can't be certain of the safety."
- *Dr. Kaul, cardiologist:* "There is a fine line between a cautious yes and abstention…I was…reassured by the enforceable REMS."
- *Dr. Rosing, NIH:* "I think there is a specific patient group that can benefit from this drug."
- *Dr. Neogi, rheumatologist:* "With the unmet clinical need in this patient population, the benefit may be sufficient for the potential risk."
- *Dr. Clegg, rheumatologist:* "Yes, for the unmet need."

Question 4. Discuss what additional studies, if any, should be conducted post-approval to further assess the safety of the product.

Panel member comments included:

- *Dr. Packer:* "Although there is considerable enthusiasm for a registry, I think it would have significant limitations and be hard to interpret…If we achieve what might be limited approval for a focused population, the sponsor may want to expand it for patients who are treated with the usual xanthine oxidase inhibitors…so I would like to see this vs. a xanthine oxidase inhibitor long-term in a meaningful number of patients."
- *FDA's Dr. Rappaport:* "The registry I was outlining in a REMS is a way of restricting the population."
- *Dr. Weisman:* "I would propose that we let the FDA know that is what we feel quite strongly about – on restricting this drug to patients with already insufficient response to febuxostat. I don't think that is necessary… not necessarily restricting it to failure of both urate-lowering drugs (allopurinol and febuxostat)."
- *Dr. Nelson:* "There are two different uses of the registry, and I think we need both of those uses implemented here. (One is) the idea of post-market surveillance use of a registry to see what happens to patients…but the other use of a registry is to prevent patient harm by…certifying physicians…really making sure these are the right patients, the right indication to get in…Over time, this could be liberalized…but in the beginning we need to ensure that we introduce the drug to the (studied) patients ...I think the registry concept is most important…Another mechanism I'd like to explore is IgE mediatedness of these infusion reactions."
- *Dr. Furberg:* "I spoke up in favor of a registry, thinking of a better designed registry…I don't like one against a historical control. I would like to see a control concurrent and to the extent possible, matched in terms of risk…An active-control study long-term would…help us get more information on efficacy and maybe more on safety. It is possible you can get away with a placebo-controlled study in other countries. I don't think you can do that in the U.S. any longer."
- *Dr. Williams:* "I was a supporter of a registry, but Dr. Packer (changed my mind)…I am concerned that we don't consider inadequately-treated gout refractory gout …We should make sure inadequately-treated gout is not

treatment-failure gout." Asked by Dr. Rappaport how long the studies should be, Dr. Williams said five years.

- *Dr. Olsen:* "A control (in the registry) is good, but it will be hard to (do) when this drug is out there."
- *Dr. Stine:* "We had our chance for a randomized trial for safety…Post-marketing won't be the same thing… Looking ahead for other drugs, we need to think more about getting safety data in the first place, or we will be stuck in this same situation again and again and again…This whole issue of a registry – we won't have a magical randomized trial in that…(I'd like) a randomized trial for safety. I don't see how that is manageable. If we approve this drug…how can you talk to someone with tophi and pain (about entering a randomized trial)?…How are you going to randomize someone?"
- *Dr. Buckley:* "One possibility might be a randomized trial where people who felt they were not responding would be continued on a drug like allopurinol or febuxostat vs. having this drug." Dr. Stine commented, "Then you don't have randomization because you are selecting on some other characteristic."
- *Dr. Kaul:* "I endorse a restricted indication registry that is enforceable…I am not too enthusiastic about registry data because it will be very difficult to dissect out the signal…If we do a randomized trial, an active control would be the proper design…(This) is a drug that no doubt is effective, but it is infused and very expensive."
- *Dr. Neogi:* "I agree it is important to limit the patients receiving (this)."
- *Dr. Mikuls:* "I'm less pessimistic about a registry than my cardiology colleagues...I understand the CV events will be difficult (to interpret)…but there are still long-term safety issues that may not arise in the first 6 months of use…and a registry does offer a mechanism to mitigate against infusion reactions…Will taking people out with SUA >6 work? Among a bigger patient population? Are there better strategies to prophylax against infusion reactions? I think those sort of things will come out with a registry – and also an enforceable REMS."

Question 5. Discuss the appropriate patient population for whom pegloticase should be indicated.

The consensus was that pegloticase should be limited to refractory gout patients.

The panel chair said, "Restricting who prescribes the drug (may be important)." Dr. Mikuls added, "There could be an argument made for failing febuxostat first."

Question 6. Discuss how patients treated with pegloticase should be monitored. For example, how frequently should uric acid levels be followed?

Dr. Weisman's comment appeared to sum up the panel sentiment: "I recommend (monitoring) the way the sponsor has done in the initial (Phase III) trial."

SAVIENT REACTION TO PANEL RECOMMENDATIONS

Savient President Paul Hamelin, RPh, spoke with reporters after the panel meeting. He deflected any suggestion that the FDA would impose a restrictive REMS – or even that the panel was calling for one.

Asked about the likelihood of a restricted access REMS, Hamelin said, "We did submit a REMS…and we also added some additional thoughts to the REMS in an amendment we filed in January (2009). We have always been very supportive …We always anticipated it. It is a healthy part of the approval process today. How it will ultimately turn out in the end, we can't predict…We heard a wide range of thoughts from the advisory committee…but ultimately it is the reviewing division's decision (the FDA's decision) on the appropriate type of REMS...and we will end up having some discussions with them (the Agency)."

Asked if he expects to have to alter the company-proposed REMS, Hamelin said, "We are open to adjustments. It is expected that there will be adjustments…We are waiting for some signals from the FDA on what they think is appropriate. We made a draft and will hopefully have some dialog."

Asked what a restricted registry means to him, Hamelin said, "We heard a wide range of ideas…The Agency will probably approach us in the next few weeks or months."

Asked if restricted access would be problematic, Hamelin said, "We are committed to working with the Agency to get the drug approved and make it available…I have seen very few drugs with this kind of dramatic clinical benefit in as early as 13 weeks."

Asked about the outlook for FDA approval by the August 1, 2009, PDUFA date, Hamelin said, "We try to be as cooperative and responsive as we can…The initiative is on their (the FDA's) part…All signals and indications which they have given is August 1 (2009)."

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