NEWS FROM THE FDA

Panel Votes in Favor of MRSA Antimicrobial

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COLLEGE PARK, MD. — Clinical trial data indicate that the antibiotic telavancin is safe and effective for treating complicated skin and skin structure infections, including those caused by methicillin-resistant *Staphylococcus aureus*, the majority of a federal advisory panel agreed.

The Food and Drug Administration's anti-infective drugs advisory committee voted 21-5 regarding the safety and efficacy of telavancin. Those voting in favor said that while they were concerned about nephrotoxicity, QT prolongation, and possible teratogenic effects associated with the drug, they believed these risks were manageable.

The panel voted 18-5, with 3 abstentions, that there could be clinical situations in which the benefits of telavancin in pregnant women would outweigh its risks. All but one panelist agreed that a risk management strategy was needed to prevent unintended use in pregnant women or in women of childbearing potential.

Telavancin was teratogenic in animal studies, which found it was associated with limb malformations in three animal species, but there are no human data available. The FDA's analysis concluded that these findings "strongly" support that these effects are drug-related.

Theravance Inc., the drug's manufacturer, has developed a risk management plan designed to minimize pregnancy exposures, the risk of nephrotoxicity, and the risk related to QT prolongation, and has proposed that the drug not be used during pregnancy unless the benefit to the patient outweighs the potential risks to the fetus.

The plan also includes recommendations to adjust the dose based on creatinine clearance and avoid the drug in patients with conditions such as congenital long QT syndrome and uncompensated heart failure.

Those voting no on the safety and efficacy question cited concerns about the association of the drug with more than one toxicity, "Safety concerns in multiple systems, not just one, complicate risk management," said the acting panel chair, Dr. L. Barth Reller, professor of medicine and pathology at Duke University, Durham, N.C.

The proposed indication for is for the treatment of complicated skin and skin structure infections (cSSSI) caused by *Staphylococcus aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, the *Streptococcus anginosus* group, and *Enterococcus faecalis*.

For approval, the company submitted the results of two double-blind, randomized phase III noninferiority studies of almost 1,800 adults with cSSSI caused by gram-positive bacteria, enrolled from 2005 to 2006. (Half of the 1,320 patients with microbiologic confirmation of pathogens at baseline had MRSA.) Patients were treated with telavancin (10 mg/kg IV once daily) or vancomycin (1 g IV every 12 hours).

FDA and company analyses of different outcome measures indicated that in both studies treatment with telavancin for 7-14 days was as effective as treatment with vancomycin. Efficacy against MRSA infections was slightly better among those treated with telavancin, but the difference was not significant.

Telavancin was associated with common adverse events that were mostly mild or moderate. The rate of renal adverse events among those on telavancin was 3.4%, compared with 1.2% among those on vancomycin; the rate of severe renal adverse events also was higher among those on telavancin (1.2% vs. 0.4%, respectively). Renal events were associated with comorbidities such as heart failure or kidney disease at baseline, according to Theravance.

The company is recommending that serum creatinine be monitored during treatment and that the potential risks of the drug be weighed against the benefits in patients with moderate or severe renal impairment or conditions that predispose them to kidney dysfunction.

Cardiac-related severe adverse events were similar among those on telavancin and vancomycin (11% in both groups). There were four patients on telavancin and six on vancomycin who had a fatal cardiac event; in two cases in the telavancin group, the investigator considered that the deaths were possibly related to the drug, according to the FDA.

In October 2007, the FDA issued an approvable letter for telavancin, which indicated the agency's preparedness to approve the product after the outstanding questions specified in the letter are resolved. ■

Safety Has Been 'Well Established'

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Bimatoprost is thought to prolong the growth cycle of hair and increase melanin synthesis, resulting in longer, thicker, and darker eyelashes, according to Allergan. Allergan pursued development of the cosmetic indication, using the same formulation and dose, and developed a 4-point Global Eyelash Assessment (GEA) score. The investigator-rated scale ranks the prominence of a person's upper eyelashes ranging from minimal to very marked, evaluating length, fullness, and color, with length considered the most important feature.

Because of the large safety database available, the FDA agreed that the safety of bimatoprost solution had been "well established," and asked the company to conduct a safety and efficacy trial for the indication.

The study compared the eyelash-enhancing effects of the once-daily application of bimatoprost solution to the margin of the upper eyelid in a study of 137 people who were given the drug and 141 people who were given a placebo. The patients were between the ages of 22 and 78 years (mean age 50 years), were mostly female, and had a baseline GEA score of 1 or 2. Most were white; the rest were mostly Hispanics and Asians, the one African American in the study was in the vehicle group. When applied directly to the margin of the upper eyelid, the dose that ends up in the eye is about 5% the amount resulting from the dose administered directly in the eye for glaucoma, according to Allergan.

After 16 weeks, 78% of those in the bimatoprost group had at least a 1-point increase in their GEA score, the primary efficacy end point, compared with 18% of placebo patients. At that time, 33% of those in the treatment group had at least a 2-point improvement, compared with 1% of the placebo group. Both were highly statistically significant differences. Patient satisfaction scores at the end of the study also were significantly greater among the treated patients.

After 16 weeks, 78% of bimatoprost-treated patients had at least a 1-point increase in their global eyelash score.

There were no clinically relevant changes in intraocular pressure among treated patients. One adverse event that was significantly more common among those treated with bimatoprost than with the vehicle was conjunctival hyperemia (3.6% vs. 0). This is a common side effect among glaucoma patients treated with bimatoprost that typically resolves within a few weeks, which was also observed in this study, according to Allergan. About 3% of those in the treatment group had hyperpigmentation of the skin, vs. 0.7% among vehicle; this is reversible once treatment is stopped, the company noted.

There was also one case of iris hyperpigmentation in a bimatoprost-treated patient; this is not reversible, said Dr. Sef Kurstjens, chief medical officer at Allergan. He cited studies that indicate that bimatoprost-associated hyperpigmentation of the skin and iris is caused by an increase in melanin, with no cell proliferation or atypia.

None of the three serious adverse events in the study (one case of lymphoma and a case of recurrent breast cancer in the vehicle group and a case of squamous cell carcinoma on the back in the treatment group) were considered treatment related. Four patients in the treatment group discontinued treatment because of an adverse event, of which three—eczematous changes, irritant dermatitis, and eye inflammation—were considered related to treatment.

One of the panel members, Dr. M. Roy Wilson, chancellor and professor of ophthalmology, University of Colorado, Denver, said there was no question that the product increases eyelash growth, and that he agreed that the risk-benefit profile was favorable for the cosmetic indication because of the preponderance of data of bimatoprost in patients with glaucoma and because application to the eyelid results in less exposure to the eye. Although the lack of black patients was a major weakness of the study, he said he had no concerns about its use in people of color, because the amount of data in glaucoma patients cannot be ignored, added Dr. Wilson, a glaucoma specialist.

More than half the panel recommended that Allergan conduct postmarketing studies, including studies that track long-term use, especially by younger people; and explore its effects in patients with disease-related loss of eyelashes. Another of the panel's concerns was off-label use of the product, especially among adolescents.

The panel's recommendations for product labeling included explanation that there is a potential for iris pigmentation, and that bimatoprost needs to be continued to maintain the effect. (Eyelash growth plateaus and returns to baseline about 3-4 months after treatment is stopped, according to Dr. Scott Whitcup, head of research and development at Allergan.)

No patients with eyelash loss caused by a disease or chemotherapy were included in the study, but there is anecdotal evidence that bimatoprost can increase the growth of eyelashes in these populations and the company plans to study these groups in the future, Dr. Whitcup said. Panelist Dr. Marijean Miller, an ophthalmologist at Children's National Medical Center, Washington, said that, although there are no pediatric data on its cosmetic use, she sees a potential role for bimatoprost in children who have no eyelashes following chemotherapy or because of an illness, and would not want it entirely excluded for use in children. However, she added, "it's those teenagers substituting it for mascara who scare me."

She said that the finding that treatment increases the size of melanocytes, but not atypia was "reassuring."

The FDA usually follows the advice of its panels, which are nonbinding. ■