FDA Calls for Research on New IV Antibiotic

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COLLEGE PARK, MD. — The Food and Drug Administration has requested that a well-controlled clinical trial with an adequate number of patients with methicillin-resistant *Staphylococcus aureus* be conducted before the lipoglycopeptide antibiotic oritavancin is approved, according to the manufacturer.

The FDA made the request in a "complete response letter" to Targanta Therapeutics Corp. regarding its application for approval of oritavancin, the company said. The FDA's Anti-Infective Drugs Advisory Committee had voted 10-8 that data from two clinical trials of oritavancin failed to show that it is an effective and safe treatment for complicated skin and skin structure infections (cSSSIs), citing the need for more evidence to prove its efficacy against methicillin-resistant *Staphylococcus aureus* (MRSA).

Dr. Carol A. Kauffman, chief of infectious diseases, Veterans Affairs Health Care System, Ann Arbor, Mich., was among the majority voting no on the safety and efficacy question. "It may be a wonderful drug," she said, but more information is needed. She urged the FDA to encourage Targanta to conduct a study of the drug in MRSA patients.

In the letter, the FDA said that the company had not shown the safety and efficacy of oritavancin for the proposed indication, according to Targanta. At the meeting, the FDA panel reviewed two studies submitted by Targanta, which compared oritavancin with vancomycin in approximately 2,000 adults with cSSSIs. Oritavancin inhibits cell wall biosynthesis with a mechanism of action similar to that of vancomycin but also disrupts the membranes of gram-positive bacteria and is active against gram-positive bacteria, including MRSA, according to Targanta.

The company has proposed that oritavancin be approved for treating adults with cSSSIs caused by susceptible isolates of the gram-positive organisms *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, the *Streptococcus anginosus* group, *Streptococcus dysgalactiae*, and *Enterococcus faecalis* (vancomycin-susceptible strains only). The recommended dosing regimen is 200 mg (300 mg for people who weigh more than 110 kg) daily for 3-7 days. It is administered in an intravenous infusion over 60 minutes.

In two randomized, double-blind phase III studies of approximately 2,000 adults with a cSSSI presumed or proved to be caused by gram-positive bacteria, the overall efficacy of once-daily treatment with oritavancin for 3-7 days was similar to a regimen of intravenous vancomycin twice a day for 3-7 days followed by daily oral cephalexin for a total of 10-14 days, with a low rate of relapse, the company said.

One study used a weight-based dose of oritavancin; the larger study used the fixed dose that is the proposed dose. A majority (10 of 18 panelists) voted that the weight-based dosing study did not provide independent evidence that oritavancin is effective for cSSSI, largely because the study was too small, was underpowered, and did not include enough MRSA cases.

In an 11-6 vote with 1 abstention, the panel voted that the larger study provided evidence that oritavancin was effective for cSSSI. However, several of those voting yes said that, while they agreed that the study showed oritavancin's overall effectiveness, they did not believe the study showed the drug was effective against cSSSI due to MRSA specifically. Those voting no expressed concern that there was insufficient evidence that oritavancin is effective against MRSA, the cause of most cases of cSSSI, and because it had not been studied in infections caused by contemporary isolates of MRSA (the study was conducted between 1998 and 2002).

In the fixed-dose study, the efficacy rate was about 12% lower among those infections identified as MRSA in the oritavancin arms, compared with those in the vancomycin arm, according to the FDA's presentation of the data.

The safety profiles of both regimens, including the number of deaths and significant adverse events, were comparable, although the rate of treatment-emergent adverse events was statistically lower among those on oritavancin. ■