# Trends-in-Medicine

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# Quick Pulse



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## ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE RECOMMENDS LABEL EXPANSION FOR CUBIST PHARMACEUTICALS' CUBICIN (DAPTOMYCIN)

Rockville, MD
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Cubist filed an sNDA for Cubicin in September 2005, seeking a label expansion for Cubicin to include community-associated methicillin-resistant *S. aureus* (CA-MRSA). The FDA granted priority review in November 2005, and the Agency's action date is March 29, 2006. With a unanimous advisory committee vote in favor of approval, FDA approval looks almost certain.

The proposed indication is: *S. aureus* bacteremia (SAB), including patients with known or suspected endocarditis caused by methicillin-susceptible and methicillin-resistant strains. The proposed dose is 6 mg/kg monotherapy administered as a 30-minute IV infusion once daily for a minimum duration of 2-6 weeks, depending on the clinical condition.

The advisory committee was divided on how it should be labeled. Panel members agreed that treatment of both uncomplicated and complicated bacteremia should be indicated, but they didn't agree on whether the label should specify infective endocarditis as well.

Several antibiotics – all available as generics – are currently approved to treat endocarditis and bacteremia:

- Imipenem
- Cefazolin
- Gentamicin
- Vancomycin
- Nafcillin
- Oxacillin

However, all of these were approved more than 14 years ago. No anti-infectives have been approved for endocarditis since 1992, when the FDA issued new guidance for approval of these drugs. Dr. Janice Soreth, Director of the Division of Anti-Infective and Ophthalmology Products, commented, "What we wrote that we thought would be doable turned out to be a barrier (to approval)." The guidance called for a relatively small, non-comparator trial with a reasonable mix of patients:

- A mix of artificial and native valves, right- and left-sided disease, and acute vs. subacute clinical presentations, or the label will be restricted to just those types of infection and populations actually studied.

- One open trial of at least 50 patients that establishes a pre-determined overall clinical and microbiological success rate.
- At least two investigators in different geographic areas for any trial.

In 2004, this same advisory panel recommended that the FDA re-write the guidance on catheter-related bloodstream infections in light of current health needs and drug development resources, balancing good science with the practicalities of clinical trial design and conduct. The panel also recommended that *S. aureus* bacteremia patients with and without identified sites of infection be studied. The FDA acknowledged that the Cubist Cubicin trial was designed with these recommendations in mind and with Agency approval.

Dr. Soreth suggested that this advisory committee meeting is designed to help clarify the path for other sponsors with other drugs as well as vote on the approval of Cubicin. She said, "In a discussion of this trial we will learn more about this drug and more about the complexities and issues associated with *S. aureus* and endocarditis which will further inform us should other sponsors rise to the challenge to conduct a study in this area with already marketed drugs or drugs still in development."

An FDA consultant, Dr. John Edwards Jr., Chief of Infectious Disease at UCLA School of Medicine, described the increasing incidence of sepsis in general and gram-positive sepsis in particular in the U.S. He said the emergence of CA-MRSA has become a major cause of healthcare-associated bloodstream infections, including necrotizing fasciitis, severe sepsis, pneumonia, empyema, and musculoskeletal infections. Both hospital-related and community-acquired MRSA are intermingling and increasing – and there is increasing *S. aureus* resistance to vancomycin.

*S. aureus* is now the most common cause of endocarditis, which is increasing worldwide. He pointed out that *Staphylococcal* endocarditis is associated with modern healthcare advances, citing a steady increase from 1990-1999 in cardiac device infections among Medicare beneficiaries. He said that it is clear that if a patient has any kind of device implanted and develops a bacterial infection, the risk of MRSA increases substantially.

## CUBIST PRESENTATION

Dr. Henry Chambers, Chief of Infectious Diseases at the University of California, San Francisco, opened the company presentation with a review of management issues in the treatment of patients with *S. aureus* bacteremia, including the risk of poor outcome, choice of antibiotic, and duration of therapy. He commented, "Oral therapy (for MRSA) is not ready for prime time…The current armamentarium is inadequate for outpatient treatment, MRSA, and patients who fail or cannot tolerate therapy…Physicians must rely on drugs not approved for treatment of complicated staphylococcal infections, drugs of unknown or poorly documented efficacy, second-line agents, and combinations of agents of uncertain benefit."

**Factors Affecting Choice of Antibiotic**

| Antibiotic | Dosing | Pros | Cons |
|---|---|---|---|
| Nafcillin or oxacillin | 2 g q4h IV | Highly effective | Poorly tolerated, inconvenient |
| Cefazolin | 2 g q8h IV | Effective | Inconvenient |
| Vancomycin | 1 g q12h IV | Well tolerated, convenient | Less effective than β-lactams |
| Dicloxacillin or cephalexin | 1 g qid PO | Convenient (oral) | Unknown efficacy, intolerable GI side effects, qid dosing |

**Duration of Therapy**

| Length of treatment | When appropriate |
|---|---|
| 7-10 days | Associated with high relapse, complication rates |
| 10-14 days | Standard recommended duration |
| 4-6 weeks | For endocarditis, osteomyelitis, complicated *S. aureus* bacteremia |

David Mantus PhD, Vice President of Regulatory Affairs for Cubist, stressed that >150,000 patients have been treated with

**Pivotal Cubicin Trial Efficacy Results (by ITT)**

| Measurement | Cubicin | Standard-of-care comparator |
|---|---|---|
| **By ITT** | | |
| Patients by ITT | 120 patients | 115 patients |
| ***Primary endpoint #1:*** Success at Test of Cure | 44.2% | 41.7% |
| ***Primary endpoint #2a:*** Success in MRSA | 44.4% | 32.6% |
| ***Primary endpoint #2b:*** Success in MSSA | 44.6% | 46.7% |
| ***Primary endpoint #2c:*** Success based on definite or possible endocarditis diagnosis at entry | 45.6% | 40.7% |
| ***Primary endpoint #2d:*** Success based on no endocarditis diagnosis at entry | 40.0% | 45.8% |
| Success at Test of Cure in right-sided endocarditis (by adjudication committee) | 42.1% | 43.8% |
| ***Primary endpoint #3:*** Success at end of therapy | 61.7% | 60.9% |
| Time to clearance of SAB | 5 days | 4 days |
| **Per protocol** | | |
| Patients per protocol | 79 patients | 60 patients |
| ***Primary endpoint #1:*** Success at Test of Cure | 54.4% | 53.3% |
| ***Primary endpoint #2:*** Success in MRSA/MSSA | 44.6% | 46.7% |

Cubicin, with no new toxicities being reported and about one-third of doses delivered in the outpatient setting. He estimated that 25% of Cubicin use is off-label for bacteremia, with about 50% of this at the 4 mg/kg dose that was approved for skin – not the 6 mg/kg doses studied in *S. aureus* bacteremia.

Dr. Helen Whamond Boucher, Director of Infectious Diseases at Tufts University – New England Medical Center, presented the results of the 180-patient, non-inferiority pivotal study, which was conducted at 44 sites in four countries. In the trial, 236 patients were treated (200 in the U.S. and 36 in Europe), with 157 completing therapy. She pointed out that non-inferiority was shown in the primary endpoints.

Jeff Alder PhD, Vice President of Drug Discovery and Evaluation at Cubist, reviewed the MIC (minimum inhibitory concentration) shifts to ≥2 µg/mL that were seen in the Cubicin pivotal trial. He noted that MICs of 2 µg/mL were observed prior to the original approval of Cubicin, and he stressed that in the pivotal trial MIC ≥2 occurred in an equal number of vancomycin-treated patients as Cubicin-treated patients. Cubist conducted extensive studies to understand this, concluding that drug exposure and concentration are not likely a factor. Rather, he said, patient-specific factors play a large role, particularly complicated infections and outcomes, but adjunctive care is important. Dr. Alder said, "The drug, the bug, and the patient were investigated. No decisive bacterial or daptomycin factors were identified that accounted for large MIC increases…What can be said for patients with MIC increases is that the infections were complicated. Additional adjunctive care was needed and not received."

**Pivotal Cubicin Trial Safety Results (by ITT)**

| Measurement | Cubicin n=120 | Comparator n=116 |
|---|---|---|
| Any adverse event | 95.8% | 94.8% |
| Drug-related adverse event | 35.0% | 42.2% |
| Severe adverse event | 51.7% | 44.8% |
| Drug-related serious adverse event | 2.5% | 5.2% |
| Deaths | 15.0% | 16.4% |
| **Discontinuation due to adverse events** | | |
| All | 16.7% | 18.1% |
| Drug-related adverse events | 8.3% | 11.2% |
| Rashes and hypersensitivity reactions | 2.5% | 7.8% |
| CPK increased | 2.5% | 0 |
| Interstitial nephritis and renal failure | <1% | 3.4% |
| **Common adverse event** | | |
| Anemia | 12.5% | 15.5% |
| Diarrhea | 11.7% | 18.1% |
| Vomiting | 11.7% | 12.9% |
| Constipation | 10.8% | 12.1% |
| Nausea | 10.0% | 19.8% |
| Hypokalemia | 9.2% | 12.9% |
| Peripheral edema | 6.7% | 13.8% |
| Headache | 6.7% | 10.3% |
| Arthralgia | 3.3% | 11.2% |
| Musculoskeletal and connective tissue disorders | 29.2% | 36.2% |
| Rhabdomyolysis | 1 patient | 0 |
| **Renal impairment** | | |
| At least one adverse event | 6.7% | 18.1% |
| At least one serious adverse event | <1.0% | 7.8% |
| Discontinuations | <1.0% | 4.3% |
| Renal and urinary disorders in patients treated ≥28 days | 14.8% | 31.0% |

Dr. Gloria Vigliani, Vice President of Medical Strategy at Cubist, reviewed the safety of Cubicin. She said the data showed that:

- Cubicin is well tolerated at 6 mg/kg QD, with no new safety issues.
- Skeletal muscle effects are uncommon, reversible, and can be monitored.
- Comparator agents are associated with significant renal toxicity.

Dr. G. Ralph Corey, Professor of Infectious Diseases at Duke University, concluded the Cubist presentation with a plea to the panel for a new treatment option – Cubicin – for the increasingly serious problem of *S. aureus* infections. He suggested the high off-label use of Cubicin may be due to frustration with a lack of options, "*S. aureus* is being tested by clinicians in a non-structured setting."

## PANEL DISCUSSION

After the Cubist presentation, the panel questioned the company for about an hour, focusing on three topics:

1. **Relatively small size of the trial.** The last drug approved for endocarditis was approved on the basis of data from 11 patients, and placebo-controlled trials are impossible in this patient population, so the size of the trial did not appear a major issue. The panel had questions about the design and analysis of the trial to determine the consistency of the data and the strength of the company's conclusions. The panel appeared satisfied with the company's answers.
2. **Drug resistance (MIC ≥2 µg/mL).** There is more MIC with Cubicin than vancomycin, and the panel is concerned about whether this emerges during treatment and how often.
3. **Safety** in terms of:
   - CPK elevation.
   - Skeletal muscle side effects (one case of rhabdomyolysis).

### FDA PRESENTATION

Dr. Alfred (Fred) Sorbello, an FDA Medical Officer, outlined these issues of concern to the review team:

1. A worrisome number of patients had a shift in MIC from baseline to higher levels during the course of treatment with Cubicin. There were increasing MICs to Cubicin during Cubicin therapy, with an increased likelihood of failure at the primary efficacy endpoint. The increasing MICs were also associated with penicillin-resistant *S. aureus* (PRSA) and subsequent death.
2. The reliability of the endocarditis diagnosis was questioned.
3. PRSA was more frequent among failures in the Cubicin group.
4. The generalizability of the efficacy data from the all-comers population to the endocarditis subgroup was problematic in terms of pathophysiology, adjunctive therapy, and prognosis. Furthermore the overall point estimates for success were low. There were low efficacy rates in both treatment groups.
5. The endocarditis population was small and insufficiently powered to permit statistically meaningful conclusions.

**FDA Analysis of Mortality**

| Length of treatment | Cubicin | Comparator |
|---|---|---|
| All-cause mortality rate | 15.0% | 16.4% |
| Proportionate mortality rate associated with PRSA | 44.4% | 36.8% |
| Mortality rate associated with PRSA | 66.6% (relative risk 1.10) | 60.2% |
| Deaths up to Day 42 | 12.5% | 11.2% |
| Deaths to end of study | 15% | 16.4% |

Peter Coderre PhD, an FDA microbiologist, discussed the increase in MICs, noting that:

- Increasing Cubicin MICs were documents *in vitro*, *in vivo*, in the literature, and during the pivotal clinical trial. And he said that clinical failures in Cubicin patients increased with an increase in MICs. Surveillance data also show increasing Cubicin failures with increased MICs.
- Currently, *S. aureus* isolates with a MIC ≤1 are considered susceptible to Cubicin.
- Breakpoints for intermediate and resistant isolates have yet to be established.

*Will resistance to Cubicin become a major clinical problem?* He suggested it will.

- Among all-comers in the pivotal trial, increasing Cubicin MICs occurred among clinical failures.
- In surveillance data, there is evidence of increasing Cubicin MICs over time, and there have been more reports in the literature (2005-2006) showing Cubicin resistance.
- *In vivo* data show Cubicin is more efficacious than vancomycin but that there is diminished Cubicin susceptibility during therapy.
- *In vitro* data indicate bacteria develop resistance at sub-inhibitory concentrations. There is cross-resistance to nisin but not vancomycin or ampicillin.

Dr. Charles Cooper, another FDA Medical Officer, focused on three issues:

1. **Infection-related serious adverse events,** which were more frequent with Cubicin than the comparator. This may be related to an underlying disease process or a propensity for gram-negative infections.
2. **CPK elevation.** More patients on Cubicin had an increase of >500 U/L for baseline. There is a possible association with prior or concomitant treatment with a statin.
2. **Renal toxicity.** There are similar rates of percentage increase in creatinine from baseline.

### THE FDA QUESTIONS TO THE PANEL

**QUESTION 1. Do data from the pivotal study provide substantial evidence of safety and efficacy of daptomycin in the treatment of *S. aureus* bacteremia?**
**Unanimously Yes**

*Please include in your deliberations a discussion of the significance of patients with persistent or relapsing bacteremias and whose staphylococcal isolates had increasing MICs to daptomycin. Are there specific comments that you have regarding the product label?*

Panel members urged the FDA to:

- Specify the dose should be 6 mg/kg, not the 4 mg/kg that people are currently using off-label.
- Require or recommend regularly monitoring of CPK and MIC.

Panel member comments included:

- "The MICs increasing are clinically significant, particularly in patients with complicated bacteremias and certainly endocarditis…I question whether there is evidence to use (Cubicin) in LIE (left infective endocarditis) and only reservedly in RIE (right infective endocarditis). Even in complicated bacteremia I think MIC should be monitored at least weekly and perhaps more frequently if there is evidence of persistence of bacteremia or non-clinical response."
- "The sponsors should be commended on a very good study. There is substantial evidence of safety…I was shocked at how low the success rate was…but the data do

support (approval)…More and more, I'm asked to approve the discharge of a patient on vancomycin QD with no data at all, so at least we have some good data on Cubicin (QD), and that is very reassuring to me."

- "I am concerned about the rise of MICs, but we have to monitor at the bedside as we do with all patients who have serious bacteremias. I would agree that we have to do another study and prospectively define what PRSA is and not leave that to each individual investigator…It would also be useful to have some data on what type of metastatic infections we do have with bacteremia because that can help with understating the duration of bacteremia. The original recommendation of 4-6 weeks treatment was to treat metastatic infections, and until we have a better handle on that, we still won't know how long to treat these infections."
- *Patient representative:* "I think some resistance will eventually show up, but, unfortunately, that is the nature of *S. aureus*. The label should state that daptomycin should be used very judiciously, coupled with good cultures and sensitivity techniques, just like vancomycin."
- *Consumer representative:* "I'm not convinced the two drugs were on a level playing field on MICs…Probably there was more scrutiny for daptomycin than the vancomycin arm…When we see increasing MICs, we may have pushed the drug to the limit, and it is time for surgical intervention or something beyond simple medical management."
- "I wish there were something better, but it (Cubicin) certainly demonstrated non-inferiority. I think CA-MRSA is a different creature than hospital-acquired MRSA or MSSA…It may well be the natural history of clearance of that organism and complications are going to be different, and it will be tougher to treat, so to have drugs to treat that will be a greater challenge."
- *Biostatistician:* "I think the label should emphasize the appropriate dose and not under dosing. I also think there is substantial evidence of safety and efficacy, and MICs may be increasing with all anti-infectives."
- "This drug looks like it is not necessarily better than vancomycin but not inferior, and there is really need for new, even more effective therapies, so the door is still wide open for better investigations and new drugs."

**QUESTION 2. Do data from this study provide substantial evidence of safety and efficacy of daptomycin in the treatment of patients with infective endocarditis (IE)? Yes 5, No 4**

The panel was divided on whether the efficacy results in the all-comers population with *S. aureus* bacteremia can be extrapolated to patients with infective endocarditis.

An FDA official also asked the panel to provide more guidance on labeling, saying that in the label the Agency could say:

- Nothing.
- Complicated bacteremia.
- It has not demonstrated safety and efficacy in endocarditis.
- Cubicin is contraindicated in endocarditis.
- There is limited experience in bacterial endocarditis, and if the drug is used, it should be used with frequent monitoring.

Dr. Jeff Borer, Chief of Cardiovascular Pathophysiology at Weill Medical College of Cornell University, a **non-voting consultant** on the panel offered this opinion: "I think it can be extrapolated to infectious endocarditis…The question of efficacy in endocarditis is confounded by the fact that the diagnosis is very difficult to make…This is a population at high risk for disaster at the front-end, and you have to treat them with something without knowing the precise diagnosis. The standard for comparison is not the best. The best standard would be opening the patient, looking at the valve, taking a piece out, and sending it to the path lab – which, of course, we can't do…The issue of LIE is a problem, but…the drug didn't do any worse than comparator…I don't think it would be necessary to be so terribly pessimistic about use of Cubicin in LIE…The label can say what is and isn't known…There is substantial efficacy and acceptable safety for the intended use in IE, and that the data can be extrapolated from all-comers to IE."

Panel members responses included:

- **YES** – *Patient representative:* "The study does show efficacy vs. the comparator…I would think vancomycin itself would have a hard time passing some of the hurdles we are asking this drug to pass…Efficacy in IE is just as good as the comparator."
- **YES** – *Consumer representative:* "I feel comfortable saying yes if people are using the Duke criteria to initiate therapy. The caveat may be that clinicians need to be cautioned that there is limited data on efficacy and safety in LIE."
- **YES** – "To say it is not effective in endocarditis would (be wrong), but the label needs to say overall the efficacy is 44%. And let people know it is not greater (efficacy), that the results are based on small numbers and a mixture of different clinical entities."
- **YES** – *Chair:* "Of course, people with uncomplicated bacteremia can't be extrapolated to LIE, but RIE is pretty much the same as bacteremia…I would like us at least to have out there (advice) to use 6 mg/kg if you have bugs in your bloodstream…And as strongly as you could, you should say there is limited data and frequent monitoring is necessary in anyone thought to have LIE."

- **NO** – *Infectious disease specialist:* "My suggestion is the label should say it has been studied and is not inferior to the comparator, where the Duke entry criteria were used."
- **NO** – *Infectious disease specialist:* "(I voted no) primarily because the numbers are too small…I would hate to later defend approval in IE based on the data here…Saying that it works for complicated bacteremia for me is sufficient. I am comfortable with the statement that there is limited experience in the treatment of IE, and leave it at that."
- **NO** – *Infectious disease specialist:* "To me there aren't enough data points in the study to say this drug is at least efficacious. (It is) safe, probably, but I wouldn't use the extrapolated data from bacteremia to IE…(Cubicin) is at least as safe and efficacious as standard-of-care, but with limited experience, a definite recommendation cannot be made. If it is used in endocarditis patients, they should be monitored very carefully for treatment failures."

**QUESTION 3. Do you recommend additional studies of daptomycin in the treatment of patients with *S. aureus* bacteremia, including infective endocarditis?**
**No vote was taken**

The panel offered advice on potential trials. Dr. Borer suggested a registry instead: "Setting up a randomized trial in this is very, very difficult, and I don't think that by itself will answer some of the questions we have here. A registry would be helpful, with consecutive patients entered…The registry should have sufficient size to provide absolute potential estimates to improve the label. That would be very, very useful. It would be a lot easier to do that than to mandate another randomized trial, and it would be a more real-world estimate."

**QUESTION 4. What recommendations do you have for future studies of *S. aureus* bacteremia and endocarditis? Please include in your discussion study design issues such as case definition, specificity of diagnosis at baseline, inclusion and exclusion criteria, and endpoints.**
**No vote was taken**

Among the panel recommendations were:

- Time-specific endpoints, such as 12 weeks after randomization, instead of response to therapy, etc.
- Blinded trials.
- A better up-front definition of PRSA.
- More attention to the length of therapy. A doctor said, "It would be useful to know if there is a difference between two and three week therapy."
- Looking at MICs prospectively.

## WHAT FDA APPROVAL WOULD MEAN

A Cubist physician consultant added at the end of the meeting: "The key question for me is, 'Do I feel comfortable taking a patient who comes in with probable complicated bacteremia and put him on bacteremia (therapy) knowing he might have endocarditis?' Yes. Do I then want to continue him on the drug if he had RIE? If he had MRSA, yes. If MSSA, no, I'd switch drugs. RIE patients don't die, and LIE patients die…The failure of vancomycin in LIE is abysmal, and I think we don't have much to lose with that group, but we do with MSSA."

Cubist's Chief Scientific Officer, Dr. Frank Talley, said his company is continuing to look at other areas of unmet medical need and is in contact with the FDA and European regulators to try to design studies that would expand the Cubicin label.

Panel members, questioned after the panel adjourned, agreed that FDA approval of Cubicin would do three things:

1. Improve the comfort level for doctors who are already using Cubicin off-label.
2. Increase overall use of the drug, for bacteremia and RIE, but probably not for LIE. A panel member said, "I don't think there will be much LIE use even if the FDA allows it. I won't use Cubicin for that."
3. Allow Cubist sales reps to talk about these indications.

Where will use fall – after or before vancomycin? One panel member said, "People will look at the economics – the cost of monitoring patients, the cost of the drug, and whether patients can get out of hospital faster."

- **Drug cost.** The cost of Cubicin is at least double the cost of vancomycin. The higher cost will be able to be justified, a source said, in vancomycin failures, patients with excessive toxicity from vancomycin, and patients allergic to vancomycin. He explained, "Cubicin will not replace vancomycin. And clindamycin might be tried after vancomycin and before Cubicin, especially in children. With the current *C. difficil* outbreak, clindamycin may not be used in adults because it can give you that, but it doesn't cause *C. difficil* in children."
- **Monitoring costs.** He estimated that the cost of monitoring patients on Cubicin will be about the same as for vancomycin – each will require some similar and some different monitoring, and the total may be a wash.
- **Hospital expenses.** Some hospitals already are discharging patients on QD vancomycin, but many doctors have resisted that since vancomycin is not approved for QD dosing. For doctors and hospitals not using vancomycin QD, Cubicin may save money by allowing patients to be discharged sooner.

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