NATIONAL PHYSICIANS ALLIANCE

May 2, 2018

NCHR and NPA Comments at FDA Advisory Committee on New Treatment for Antibiotic-Resistant Bacteria

Today, the NPA joined the National Center for Health Research in comments addressing concerns on the safety and efficacy of plazomicin as a new treatment for antibiotic-resistant bacteria.

Thank you for the opportunity to speak today. I am Dr. Danielle Shapiro, I am a physician and senior fellow at the National Center for Health Research. Our research center scrutinizes scientific and medical data and provides objective health information to patients, providers and policy makers. Our statement today reflects our views and that of the National Physicians Alliance. We do not accept funding from pharmaceutical companies so we have no conflicts of interest.

Antibiotic-resistant bacteria are a major public health concern. We must address this through enforced antibiotic stewardship, infection control, and development of effective and safe antibiotics that save people from these deadly infections.

Unfortunately, the sponsor has not proven the safety or efficacy of plazomicin for patients who have limited or no treatment options. Although there is a compelling unmet need to treat these deadly infections, we cannot lower the standard to approve this drug or any other drug that fails to demonstrate safety or efficacy through appropriate clinical research and appropriate statistical methods. That is what the law requires.

We will focus on the following questions:

#1. Do the studies show that this will work when other options are limited?
In the urinary tract infection (UTI) trial, plazomicin was noninferior to the active comparator. In other words, the older, control drug was similarly effective. Since the study population could have been treated with the control drug, the study population cannot be characterized as having limited or no option. Therefore, the results provide no evidence that this newer drug will work for the intended population. Worse, the data showed a toxic effect on the kidney in 7% of patients treated with plazomicin compared to 4% in patients treated with the older, control drug. We should not accept a more toxic drug when the older drug works as well and is less toxic. Keep in mind that the goal of non-inferiority trials is to provide added benefits for patients, such as fewer adverse effects. Since a "non-inferior drug is no more efficacious, it should have some other proven benefit, such as less serious side effects.

The blood stream infection (BSI) trial also does not demonstrate that plazomicin is safe or effective. Testing the effect of plazomicin with a noninferiority study or with exploratory analysis does not demonstrate that it is effective in patients with no other options. We cannot draw conclusions about plazomicin's benefit or harms based on what the sponsor admits is "descriptive" rather than inferential data. The results are not statistically significant, meaning the results do not rule out harm for patients and could be due to chance alone.

#2. Are these results valid?

Interpreting these results, particularly the BSI trial, is difficult because data were not collected in a standardized way, most randomized patients had negative blood cultures, and the source of infection was uncertain, especially in those who had an IV catheter. Furthermore, the intended use population was not studied in these trials. So, what will plazomicin use look like in the real world? We need to clearly define the population that would be treated with this drug based on the evidence provided. We cannot extrapolate efficacy or safety from the study population – who were well treated with an existing drug — to the intended population.

#3. What evidence do we need for approval?

We cannot approve this drug based on a single noninferiority study and a failed superiority study. Studies testing drugs for "unmet medical need" of patients who have "no other options" cannot be noninferioity studies, because by definition there is another option being tested, and the new drug could even be slightly worse. And, it is not scientifically valid or ethical to base a claim of noninferiority on a failed superiority trial.

We urge the panel to recommend that FDA require additional well-designed superiority studies that use appropriate statistical methods to determine whether plazomicin cures infections and saves lives for patients who have no other options. With reliable methods, even small studies can show a clinically meaningful and significant benefit. Since there is no evidence that plazomicin works or is safe for patients who have no or limited options, approval will do more harm than good.

As you all know, once approved, the new drugs are often promoted and prescribed for a much wider patient population. This can expose tens of thousands of patients to drugs that don't work and cause harm. Simply labeling a drug as "Limited Population" is not sufficient to limit a drug's use to appropriate patients.

Thank you for the opportunity to share our perspective.

Link to these comments via the National Center for Health Research

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