CYSTIC FIBROSIS FOUNDATION®

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Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Review

Sally Seymour, M.D.
Acting Director, Division of Pulmonary, Allergy, and Rheumatology Products

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

Dear Dr. Woodcock and Dr. Seymour:

On behalf of the 30,000 Americans with cystic fibrosis (CF), I write to call your attention to the amazing hope on the horizon for people living with this rare genetic disorder. As I'm sure you are aware, in the near future Vertex Pharmaceuticals plans to submit to the Food and Drug Administration (FDA) a new drug application for a novel cystic fibrosis transmembrane conductance (CFTR) modulator 3-drug combination product. Late stage clinical trials have demonstrated remarkable results for this new CFTR modulator combination. If approved, the product could result over time in more than 90 percent of people with CF having highly effective treatment for their specific genetic mutations. This milestone was inconceivable even just a decade ago and represents a transformational step in the fight against CF. Because of this promise, we have a great sense of urgency to help all people with CF that may benefit from this new product to have it available to them for treatment as quickly as possible. Available data suggest that highly effective CFTR modulators such as this product improve and prevent loss of lung function, slow overall disease progression, and restore quality of life.

I am therefore writing today with two requests:

1) That you move as quickly and efficiently in review of this new drug product as is possible, just as you did in the past for the review of ivacaftor (Kalydeco).

2) That you develop drug labeling to reflect the substantial evidence that this new CFTR modulator combination is highly effective as long as a patient has at least a single *F508del* mutation (no matter what their second CFTR mutation is). A welcome result of this approach would be to avoid a long and cumbersome list of CFTR mutations in the final labeling package.

Existing need in the CF population

As mentioned above, CFTR modulator therapies mark a significant advance in treatment of cystic fibrosis, as the drugs target the underlying cause of CF rather than just addressing the symptoms and clinical manifestations. CFTR modulator therapies present an opportunity to preserve health and lung function in eligible individuals with CF by slowing the progression of the disease and preventing hospitalizations, declining health status, deteriorating quality of life, and premature death.

The currently approved CFTR modulators are the best available treatment for many people with CF, however the vast majority of CF patients desperately await the increased efficacy promised by the trial results of this next generation of drugs. Despite the availability of other CFTR modulators, there is still a substantial unmet need in the CF population. Patients with a single copy of the *F508del* mutation and a minimal function mutation on the other allele currently have no drug to treat their underlying condition. Patients with two copies of the *F508del* mutation have current CFTR modulators as an option, however the demonstrated modest clinical effects for *F508del* homozygotes have left many desperate for a further advance. Together these two groups make up nearly 70% of people with CF; when assessing the population for all patients with one or two F508del mutations, that number rises to over 85%.

Promise of next generation CFTR modulator

The data from the clinical trial results for Vertex's new CFTR modulator product demonstrate gains in lung function of fourteen percentage points or greater over placebo, and ten percentage points or more over tezacaftor/ivacaftor *(Symdeko)*. These gains represent transformative levels of effectiveness over existing therapies and highlight the need for as rapid and efficient of a review as possible.

Population eligible for new modulator product

One of the challenges in CF drug development and labeling is the large number of pathologic mutations in the CFTR gene. To date, scientists have found more than 1,700 different variants of the CF gene, many of which are extremely rare and may only be found in a handful of people with CF. In fact, nearly one-third of U.S. CF patients have one mutation that fewer than 50 living CF adults in the U.S. carry.

One of the reasons we are particularly excited about the new Vertex modulator product is because it has been tested extensively in clinical trials in people with one *F508del* mutation and one "minimal function" mutation (meaning a mutation that does not produce functional protein). A large number of different versions of minimal function mutations were represented in the trial. Based on both these clinical results and earlier in-vitro results, it is clear that the Vertex combination product will be highly effective in treating anyone with a single copy of *F508del* regardless of the mutation on the other allele. Another way of thinking about this is that any CF patient with a single *F508del* mutation and a second mutation not currently approved for a modulator will benefit.

Given these data, we encourage the FDA to develop drug labeling that will reflect such a population and avoid current mutation-specific labeling practices. Doing so would avoid the need to list hundreds of "minimal function" mutations, the confusion caused by doing so, and the need to subsequently study individuals with an *F508del* mutation and a very rare unstudied mutations on the other allele. Given the very large number of genetic mutations in CF and good safety profile of the drug in clinical trials, we believe that adopting this approach would save significant work both for the FDA and the sponsor, avoid confusion for prescribers, and provide faster access to people with CF who could benefit from this new drug.

In addition, it is also clear based on both in-vitro data and clinical trial data that even in those patients with a single *F508del* mutation and a second mutation that is currently eligible for treatment with a modulator, the new Vertex modulator combination product will be clearly superior to existing therapy for all but the small subset of patients with the highly ivacaftor-responsive gating mutations that are currently listed on the ivacaftor label (5% of CF patients in the U.S.) These approved gating mutations are *G551D*, *G551S*, *S549N*, *S549R*, *G178R*, *G1244E*, *S1251N*, *S1255P* and *G1349D*. While this *F508del*/gating group will require further clinical study to assure that the new Vertex product demonstrates benefit over ivacaftor alone, we encourage the FDA to develop drug labeling which would make the new product immediately available for all other patients with at least one *F508del* mutation.

Conclusion

The recent remarkable clinical trial results of the new Vertex modulator combination suggest a potential new era of highly effective therapy for the majority of people with CF. Thoughtful and efficient evaluation will assure that as many patients who are desperately awaiting these treatments will be able to benefit as possible. If we can be of any assistance as you proceed with your evaluation, we would like to offer the CF Foundation as a resource to the FDA. We are grateful for your tireless work to efficiently deliver safe and effective therapies for people with cystic fibrosis.

Sincerely,

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