Pediatric Advisory Subcommittee Meeting
Proton-Pump Inhibitor (PPI) Template for Pediatric Written Requests
June 11, 2002

OVERVIEW

Background

At the June 11th meeting of the Pediatric Advisory Subcommittee meeting, the Committee will be asked to consider scientific, study-design, ethical, and other issues related to the proton-pump inhibitor (PPI) template: *Template for Written Requests for Proton-Pump Inhibitors Used in the Treatment of Gastroesophageal Reflux Disease (GERD).* This "PPI template" has been used by the Center for Drug Evaluation and Research (CDER) to issue Written Requests to pharmaceutical firms as specified under Section 111 (*Pediatric Studies of Drugs*) of the Food and Drug Administration Modernization Act of 1997 (FDAMA). The PPI template is located behind the third tab of this background package ("Sample Written Request").

The Written Requests for the proton-pump inhibitors have been issued to request studies in pediatric patients from birth to 16 years of age because FDA has concluded that information relating to the use of these drugs may produce health benefits in the pediatric population. The scientific and regulatory rationale for the template is summarized in a memorandum written by Dr. Hugo E. Gallo-Torres located behind the second tab of this background package ("Briefing Document"). Recommendations to FDA for the proton-pump inhibitor template were also provided by a pediatric gastroenterologist who serves on FDA's Gastrointestinal Drugs Advisory Committee. His consult to FDA is located behind the fifth tab of this background package ("Dr. Ferry Letter").

In addition, proton-pump inhibitors are widely used in pediatrics, as evidenced by treatment algorithms for pediatric patients with GERD that have been published in the medical literature as well as by usage data of these drugs in pediatric patients. Usage data for proton-pump inhibitors in pediatric patients are located behind the fourth tab of this background package ("Usage Data [IMS Health]").

As summarized in the briefing document by Dr. Gallo-Torres and in the appendix to the PPI template, FDA is requesting studies in pediatric patients ranging in age from birth to 16 years. The type of information requested differs for each age group.

- Safety information is requested in all age groups

- Both pharmacokinetic and pharmacodynamic information is requested for neonates, preterm infants, and pediatric patients less than one year of age. In contrast, pharmacokinetic information alone is requested for pediatric patients from 1 to 16 years of age.

- An exposure response study is requested in pediatric patients 1 to 11 years of age, inclusive.

- Formally powered efficacy studies are requested in pediatric patients less than one year of age, including in neonates and preterm infants.

Therefore, the PPI template is consistent with FDA regulations that describe when adult efficacy data can be extrapolated to pediatric patients and when they cannot. For example, the PPI template *does not* request efficacy studies in pediatric patients one year of age or older because the course of GERD in these pediatric patients is sufficiently similar to the course of GERD in adults. Moreover, the effects of proton-pump inhibitors, both beneficial and adverse, are expected to be similar in adults and in pediatric patients one year of age or older.[1]

Conversely, the PPI template *does* request efficacy studies in pediatric patients less than one year of age. These efficacy studies are requested because the course of gastroesophageal reflux disease in adults is not sufficiently similar to the course of pathological gastroesophageal reflux in pediatric patients less than one year of age to permit extrapolation of the adult efficacy data to this pediatric age group. The effects of proton-pump inhibitors, both beneficial and adverse, may also differ in adults from those in patients less than one year of age.

Issues

At the June 11th meeting, FDA will be seeking perspectives from the Advisory Committee on several issues (N.B.: Finalized questions will be sent to the Advisory Subcommittee at a later date). References are provided in the background package to facilitate discussion. For example:

1. Does the Committee agree that the effectiveness of a PPI for the treatment of pediatric patients less than one year of age cannot be extrapolated from older pediatric patients and adults?

   See the references "Gastroesophageal reflux disease in pediatrics" (references 1-4); "Gastroesophageal reflux in neonates" (references 5-10); and "Respiratory and supraesophageal manifestations of gastroesophageal reflux" (references 11-15).

[1] 21 CFR 201.57(f)(9)(iv): "FDA may approve a drug for pediatric use based on adequate and well controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. The additional information supporting pediatric use must ordinarily include data on the pharmacokinetics of the drug in the pediatric population for determination of appropriate dosage. Other information, such as data from pharmacodynamic studies of the drug in the pediatric population, data from other studies supporting the safety or effectiveness of the drug in pediatric patients, pertinent premarketing or postmarketing studies or experience, may be necessary to show that the drub can be used safely and effectively in pediatric patients…."

2. Are the designs of the efficacy studies requested for pediatric patients less than one year of age acceptable? Specifically, is a randomized withdrawal design acceptable? Is use of a placebo control acceptable? Are the endpoints acceptable? Is monitoring adequate? Are the inclusion and exclusion criteria adequate?

   In addition to the references listed above for item #1, see the references "Ethics" (references 16 and 17); "Special Study designs: Randomized –withdrawal trials" (reference 18); and "Choice of control group in clinical studies" (references 19-22).

3. Is the pharmacokinetic and pharmacodynamic information requested in the PPI template acceptable?

   See the references "Pharmacology of proton-pump inhibitors" (references 23-26).

We understand these issues are complex and appreciate your assistance in providing FDA with your best possible advice. We look forward to hearing from you on June 11th.

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