Drugs for Treatment of Partial Onset Seizures: Full Extrapolation of Efficacy from Adults to Pediatric Patients 4 Years of Age and Older

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Billy Dunn at 301-796-2250.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Clinical Pharmacology/Clinical

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Drugs for the Treatment of Partial Onset Seizures: Full Extrapolation of Effectiveness from Adults to Pediatric Patients 4 Years of Age and Older Guidance for Industry[1]

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I. INTRODUCTION

This guidance provides recommendations to sponsors on the clinical development of drugs for the treatment of partial onset seizures (POS) in pediatric patients. Specifically, this guidance addresses FDA's current thinking regarding clinical development programs that can support extrapolation of the effectiveness of drugs approved for the treatment of POS in adults to pediatric patients 4 years of age and older. This guidance does not address clinical development programs for the treatment of POS in pediatric patients less than 4 years of age. This guidance does not address the development of drugs to treat other types of seizures.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Historically, because evidence adequate to support an extrapolation approach was not available, FDA has required, under section 505(d) of the Federal Food, Drug, and Cosmetic Act, that sponsors establish effectiveness for the treatment of POS in pediatric patients by performing one or more adequate and well-controlled clinical trials in pediatric patients. The doses in these pediatric trials were generally based on body weight and age, in an effort to attain blood

[1] This guidance has been prepared by the Division of Neurology Products and the Division of Clinical Pharmacology I in the Center for Drug Evaluation and Research at the Food and Drug Administration.

concentrations similar to those found to be effective in adults. Doses were also informed by safety and tolerability data from open-label studies in the pediatric population.

Efficacy can be extrapolated from adults to pediatric patients when it is reasonable to assume that children, compared with adults, have a similar progression of disease, similar response of disease to treatment, and similar exposure-response relationship.[2] After excluding children with POS associated with epileptic encephalopathies, such as Lennox-Gastaut syndrome, the pathophysiology of POS appears similar in adults and pediatric patients 4 years of age and older.[3] Clinical trials of drugs for the treatment of POS in pediatric patients 4 years of age and older have shown a response to treatment (reduction in seizure frequency) similar to the response to treatment seen in adults. Systematic and quantitative analyses conducted by FDA, using data from clinical trials of drugs approved for the treatment of POS in both adults and pediatric patients 4 years of age and older, have shown that the relationship between exposure and response (reduction in seizure frequency) is similar in adults and pediatric patients 4 years of age and older. These analyses, conducted for drugs with a variety of putative mechanisms of action, have allowed FDA to conclude that the efficacy of drugs approved for the treatment of POS can be extrapolated from adults to pediatric patients 4 years of age and older.

III. DEVELOPMENT CONSIDERATIONS

A. Formulation Development

Children may differ from adults in many aspects of pharmacotherapy including feasibility of routes of drug administration, drug-related toxicity, and taste preferences. It is therefore essential for sponsors to formulate pediatric drugs to best suit a child's age, size, and physiologic condition. FDA encourages sponsors to explore innovative approaches to pediatric formulation development and testing.

B. Efficacy Considerations

As noted above, FDA has concluded that the effectiveness of drugs approved for the treatment of POS in adults can be extrapolated to pediatric patients 4 years of age and older. This conclusion does not apply to the treatment of POS in pediatric patients less than 4 years of age or to the treatment of other types of seizures.

[2] See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*. See also the pediatric study planning and extrapolation algorithm in the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[3] Pellock JM, Carman WJ, Thyagarajan V, Daniels T, Morris DL, and D'Cruz O, 2012, Efficacy of Antiepileptic Drugs in Adults Predicts Efficacy in Children: A Systematic Review, Neurology; 79(14):1482–1489.

C. Clinical Pharmacology/Dosing Considerations

To support extrapolation, blood concentrations of active drug/metabolites should be obtained from an adequately designed pharmacokinetic and tolerability study in which single and/or multiple doses of the investigational drug are administered in patients 4 to 16 years of age. The study should include an appropriate distribution of pediatric patients across this age range and be designed to characterize adequately the acute tolerability over a range of doses that covers drug concentrations known to be effective in adults.

Simulations should be performed to select doses expected to achieve exposures similar to those in adults. The sample size and sampling scheme should be planned carefully to enable characterization of pharmacokinetics with adequate precision.[4] Pharmacokinetic data from that study should be used to determine pediatric dosages and regimens that provide drug exposure similar to that known to be effective in adult patients with POS. Sponsors should share the results of this analysis with FDA before initiating the open-label safety studies described below.

D. Safety Considerations

Safety data generally cannot be extrapolated from adults to children. Therefore, sponsors should conduct clinical studies to characterize adequately the safety of the drug in pediatric patients 4 years of age and older with POS, with all ages well represented. Such studies can be open-label in design. In general, a minimum of 100 pediatric patients should be exposed to the drug for at least 6 months of treatment although the sponsor should determine the specific study characteristics on a case-by-case basis, depending on the expected and emerging safety profile of the drug. Dosing levels in these safety studies should be at or above those determined to be effective in the pediatric population, based on the extrapolation described above. Blood concentrations of the drug and its active major metabolites should be quantified whenever severe or serious adverse events occur in patients enrolled in the study.

[4] Wang Y, Jadhav PR, Lala M, and Gobburu JV, 2012, Clarification on Precision Criteria to Derive Sample Size When Designing Pediatric Pharmacokinetic Studies, J Clin Pharmacol, 52(10):1601–1606.