Drugs for Treatment of Partial Onset Seizures: Extrapolation of Efficacy from Adults to Pediatric Patients 1 Month of Age and Older

Guidance for Industry

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

August 2024
Clinical Pharmacology

Revision 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 efficacy of drugs approved for the treatment of POS in adults to pediatric patients 1 month of age and older. This guidance does not address the development of drugs to treat other types of seizures.

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II. BACKGROUND

Historically, because evidence 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 efficacy for the treatment of POS in pediatric patients by performing one or more adequate and well-controlled clinical studies in pediatric patients. The doses in these pediatric studies were generally based on body weight and age, in an effort to attain blood concentrations

[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. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2017-D-6821 (available at https://www.regulations.gov/docket?D=FDA-2017-D-6821). See the instructions in that docket for submitting comments on this and other Level 2 guidances.

similar to those found to be effective in adults, and 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 1 month of age and older.[3] Clinical studies of drugs for the treatment of POS in pediatric patients, some of which enrolled patients as young as 1 month of age, have shown a response to treatment (reduction in seizure frequency) similar to the response to treatment seen in adults. Initial systematic and quantitative analyses conducted by FDA, using data from clinical studies of drugs with a variety of putative mechanisms of action approved for the treatment of POS in both adults and pediatric patients, 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. Subsequent evaluation by FDA determined that POS are readily identifiable in pediatric patients down to 1 month of age and are phenomenologically and pathophysiologically very similar to those in older patients. These analyses and observations have allowed FDA to conclude that the efficacy of drugs approved for the treatment of POS can be extrapolated from adults to pediatric patients 1 month 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 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 efficacy of drugs approved for the treatment of POS in adults can be extrapolated to pediatric patients 1 month of age and older. This conclusion does not apply to the treatment of other types of seizures.

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[2] See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998). See also the draft guidances for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs, Including Biological Products* (September 2022) and *E11A Pediatric Extrapolation* (August 2022). When final, these guidances will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[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 and Dosing Considerations

To support extrapolation, blood concentrations of active drug and metabolites should be obtained from an adequately designed pharmacokinetic and tolerability study in patients 1 month 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 doses 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

Sponsors should conduct clinical studies to characterize adequately the safety of the drug in pediatric patients 1 month 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 specific study characteristics should be determined 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 exposures similar to those found to be effective in the pediatric population and that are proposed for labeling, 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.