
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DRAFT GUIDANCE

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

**February 2018
Clinical Pharmacology/Clinical**

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1 **Drugs for the Treatment of Partial Onset Seizures: Full**
2 **Extrapolation of Effectiveness from Adults**
3 **to Pediatric Patients 4 Years of Age and Older**
4 **Guidance for Industry¹**
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9 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
10 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
11 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
12 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
13 for this guidance as listed on the title page.
14

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18 **I. INTRODUCTION**
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20 This guidance provides recommendations to sponsors on the clinical development of drugs for
21 the treatment of partial onset seizures (POS) in pediatric patients. Specifically, this guidance
22 addresses FDA’s current thinking regarding clinical development programs that can support
23 extrapolation of the effectiveness of drugs approved for the treatment of POS in adults to
24 pediatric patients 4 years of age and older. This guidance does not address clinical development
25 programs for the treatment of POS in pediatric patients less than 4 years of age. This guidance
26 does not address the development of drugs to treat other types of seizures.
27

28 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
29 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
30 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
31 the word *should* in Agency guidances means that something is suggested or recommended, but
32 not required.
33
34

35 **II. BACKGROUND**
36

37 Historically, because evidence adequate to support an extrapolation approach was not available,
38 FDA has required, under section 505(d) of the Federal Food, Drug, and Cosmetic Act, that
39 sponsors establish effectiveness for the treatment of POS in pediatric patients by performing one
40 or more adequate and well-controlled clinical trials in pediatric patients. The doses in these
41 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.

Contains Nonbinding Recommendations

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

44
45 Efficacy can be extrapolated from adults to pediatric patients when it is reasonable to assume
46 that children, compared with adults, have a similar progression of disease, similar response of
47 disease to treatment, and similar exposure-response relationship.² After excluding children with
48 POS associated with epileptic encephalopathies, such as Lennox-Gastaut syndrome, the
49 pathophysiology of POS appears similar in adults and pediatric patients 4 years of age and
50 older.³ Clinical trials of drugs for the treatment of POS in pediatric patients 4 years of age and
51 older have shown a response to treatment (reduction in seizure frequency) similar to the response
52 to treatment seen in adults. Systematic and quantitative analyses conducted by FDA, using data
53 from clinical trials of drugs approved for the treatment of POS in both adults and pediatric
54 patients 4 years of age and older, have shown that the relationship between exposure and
55 response (reduction in seizure frequency) is similar in adults and pediatric patients 4 years of age
56 and older. These analyses, conducted for drugs with a variety of putative mechanisms of action,
57 have allowed FDA to conclude that the efficacy of drugs approved for the treatment of POS can
58 be extrapolated from adults to pediatric patients 4 years of age and older.

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III. DEVELOPMENT CONSIDERATIONS

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A. Formulation Development

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

70

B. Efficacy Considerations

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

77

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.

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78 **C. Clinical Pharmacology/Dosing Considerations**

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

86
87 Simulations should be performed to select doses expected to achieve exposures similar to those
88 in adults. The sample size and sampling scheme should be planned carefully to enable
89 characterization of pharmacokinetics with adequate precision.⁴ Pharmacokinetic data from that
90 study should be used to determine pediatric dosages and regimens that provide drug exposure
91 similar to that known to be effective in adult patients with POS. Sponsors should share the
92 results of this analysis with FDA before initiating the open-label safety studies described below.

93 **D. Safety Considerations**

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95
96 Safety data generally cannot be extrapolated from adults to children. Therefore, sponsors should
97 conduct clinical studies to characterize adequately the safety of the drug in pediatric patients 4
98 years of age and older with POS, with all ages well represented. Such studies can be open-label
99 in design. In general, a minimum of 100 pediatric patients should be exposed to the drug for at
100 least 6 months of treatment although the sponsor should determine the specific study
101 characteristics on a case-by-case basis, depending on the expected and emerging safety profile of
102 the drug. Dosing levels in these safety studies should be at or above those determined to be
103 effective in the pediatric population, based on the extrapolation described above. Blood
104 concentrations of the drug and its active major metabolites should be quantified whenever severe
105 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.