CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020764 and 020241/S002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20,764
Lamotrigine (Lamictal®)
5, 25, and 100 mg Chewable/Dispersible Tablets

GlaxoWellcome Inc.
Five Moore Drive
Research Triangle Park, NC

NDA 20,241/S-002
Lamictal Tablets
25, 100, 150, and 200 mg Tablets

Reviewer: Vijay K. Tammara, Ph. D.

Submission Dates:
February 23, 1998
June 23, 1998
August 3, 1998
August 6, 1998

Indication: Lennox-Gastaut Syndrome

Type of Submission: Response to Approvable Letter and Amendment

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In the submission dated February 23, the sponsor provided responses to the Agency's Approvable Letter dated December 3, 1997 and concurred with the Agency's suggestions regarding labeling associated with the use of Lamictal and adaptation of final dissolution specifications (Attachment 1).

Further, in the submission dated June 23, 1998, the sponsor provided an amendment to the original application to support a change to the proposed starting and escalation doses for Lamictal in pediatric patients with Lennox-Gastaut Syndrome.

The sponsor reported the validation of pharmacokinetic model (used to predict pediatric doses based on open-label pediatric data) using a further 508 plasma concentrations collected from 148 pediatric patients with a mean age of 8 years enrolled in 4 additional pediatric studies. The results of the validation indicated that the currently proposed Lamictal dose regimens for pediatric patients may produce plasma concentrations, during the initial weeks of treatment, which exceed the plasma concentrations produced by the currently recommended dose regimens in adults during the same treatment period. The magnitude of difference is greatest for pediatric patients on concomitant enzyme inducer antiepileptic drugs (EIAEDs) and also observed in patients taking valproate (VPA) along with EIAEDs. This is due to the fact that the elimination half-life is shorter in pediatrics than the adults (7.0 vs 14 hrs in EIAEDs group and 19 vs 27 hrs in EIAEDs plus VPA group), and hence they achieve

steady-state plasma concentrations faster than the adults during the escalation period. It was observed further that with the concomitant use of EIAEDS and VPA, Lamictal starting dose and escalation rate are risk factors for rash, in pediatric patients. As a result of these findings, the sponsor is proposing modifications in the starting dose and dose escalation for pediatric patients based on NONMEM analysis of pharmacokinetic data in children taking concomitant antiepilieptic therapy.

Up on review of the data (Attachment 2) presented by the sponsor based on NONMEM analysis (Dr. Raymond Miller helped in verifying the sponsor's NONMEM analysis) and simulation to predict plasma concentrations using current and proposed dose regimen, the reviewer concurs with the sponsor's evaluation. However, the reviewer requested the sponsor to submit any pharmacokinetic data obtained in patients (both pediatric and adults) to assess the pharmacokinetic differences during the dose escalation period using current dose regimens.

In response to the reviewer's request, sponsor provided some available pharmacokinetic data from clinical studies (Attachment 3), but reported that the patients were either overdosed (adults) or underdosed (pediatrics). However, calculating dose adjusted plasma concentrations in these patients indicated that pediatric patients would have had higher plasma concentrations than the adults, provided both adults and pediatrics received the current dose regimen.

APPEARS THIS WAY
ON ORIGINAL

Based on the above information, the sponsor's proposed changes in starting dose and dose escalation are acceptable.

Comment:

APPEARS THIS WAY
ON ORIGINAL

1) The sponsor is requested to delete the following statement on page 6 under the Age: Pediatric Patients subsection of Pharmacokinetics and Drug Metabolism portion of the Clinical Pharmacology section:

"Oral Clearance of lamotrigine was found to be a linear function of weight ..... were 16 years of age or younger".

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATION:

These submissions (NDA 20-764/NDA 20,241) have been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics' and based on the information provided, the sponsor's proposed changes in starting dose and dose escalation are acceptable. Please forward **Comment 1** and this **Recommendation** to the sponsor.

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APPEARS THIS WAY
ON ORIGINAL

/S/ - 8/24/98

Vijay K. Tammara, Ph. D.
Division of Pharmaceutical Evaluation I

RD/FT Initialed by M. Mehta, Ph. D. - /S/ 8/24/98

CC: NDA 20,764/NDA 20,241 (orig.), HFD-120, HFD-860 (Tammara, Mehta, Sahajwalla, Malinowski), CDR (for Drug Files).

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT 1

GlaxoWellcome

February 23, 1998

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
HFD-120, Woodmont II, Room 4037
1451 Rockville Pike
Rockville, MD 20852

Re: NDA 20-764; LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets
NDA 20-241; LAMICTAL® (lamotrigine) Tablets/S-002
Amendment to Pending Application: Clinical, Labeling, Chemistry
Final Safety Update
Response to Approvable Letter

Dear Dr. Leber:

Reference is made to the New Drug Application for LAMICTAL® (lamotrigine) Chewable Dispersible Tablets, the Supplemental New Drug Application (S-002) for LAMICTAL Tablets, and the Agency's APPROVABLE letter dated December 3, 1997. This amendment to these applications is intended to fully respond to the Agency's comments and requests for additional data so as to allow for approval of the applications.

GENERAL

Although we are seeking approval of 5 mg, 25 mg, and 100 mg strength LAMICTAL Chewable Dispersible Tablets, our intent is to initially introduce only the 5 mg (in sample and trade packs) and 25 mg (in sample and trade packs). Should there be a market need, a 100 mg strength tablet could subsequently be introduced to the market.

The following items address the individual requests in the approvable letter:

LABELING

As noted in the Agency's approvable letter and proposed labeling, Glaxo Wellcome concurs with the majority of the Agency's suggestions regarding changes to the box warning and related sections discussing serious dermatologic reactions associated with

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the use of LAMICTAL. Modifications to these sections are proposed which do not generally alter the intended message and in some instances strengthen the warning proposed by the Agency.

As requested, we have revised the following sections of the proposed label to reflect new information:

- **Acute Multiorgan Failure** subsection of the WARNINGS section
- **Other Adverse Events Observed During All Clinical Trials for Adult and Pediatric Patients** subsection of the ADVERSE EVENTS section
- **Information for the Patient**

The format of the DOSAGE AND ADMINISTRATION section has also been revised to clarify the presentation of the recommended dosing and titration for LAMICTAL; however, no new information has been added. Minor editing changes have also been made throughout the package insert.

To assist the Agency in reviewing our proposed labeling revision, we have included an annotated version of the labeling included in the Agency's approvable letter and a corresponding reference sheet detailing the rationale and justification for the recommended revisions.

Enclosed with this submission is the following labeling:

1. Annotated version of the proposed package insert from the Agency's December 3, 1997 approvable letter with our suggested revisions, rationale, and justification **(Attachment 1)**. Desk copies are being provided to John Feeney, M.D., Reviewing Medical Officer and Jacqueline Ware, Pharm.D., Regulatory Management Officer, under separate cover.

2. Revised proposed package insert for LAMICTAL Tablets and LAMICTAL Chewable Dispersible Tablets (without annotations) **(Attachment 2)**. Desk copies are also being provided to Drs. Feeney and Ware under separate cover.

3. A diskette containing an electronic version of the proposed package insert (without annotations or revisions) in Word 6.0 format (**Attachment 3**). This diskette is being provided in the archival copy and in the desk copies for Drs. Feeney and Ware.

4. Eighteen copies of final printed labels and cartons for the following (as **Attachment 4**):

- 5 mg sample pack (carton and label)
- 5 mg trade pack (label)
- 25 mg sample pack (carton and label)
- 25 mg trade pack (label)
- 100 mg trade pack (label)
- Seizure diary

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NOMENCLATURE

Agency Comment: "We have been advised by the CDER Labeling and Nomenclature Committee that the abbreviation "CD" has a large connection in the pharmaceutical community with sustained release dosage forms, and it is preferable the "CD" not appear as a suffix in the proprietary name of Lamictal Chewable Dispersible Tablets. Accordingly, we request that you adopt, as the proprietary name for the new dosage form of lamotrigine, Lamictal Chewable Dispersible Tablets. This request is reflected in the attached draft labeling."

Response: We acknowledge the Agency's request and agree to adopt Lamictal Chewable Dispersible Tablets as the proprietary name for this dosage form.

APPEARS THIS WAY
ON ORIGINAL

BIOPHARMACEUTICS

Agency Comment: "Based on the review of the data and rationale provided, your request for waiver of bioequivalence studies is granted for the Lamictal Chewable Dispersible Tablet 25 mg strength. Further, a site change from Greenville, North Carolina to Zebulon, North Carolina is also granted."

Response: We acknowledge your acceptance of our request for waiver of bioequivalence studies for the Lamictal Chewable Dispersible Tablet 25 mg. In addition, we acknowledge your acceptance of our request to produce commercial product at our manufacturing facilities located in Zebulon, North Carolina.

Agency Comment: "We ask that the following final dissolution methodology and specifications be adopted for Lamictal Chewable Dispersible Tablets, 5 mg, 25 mg, and 100 mg:"

Apparatus:	USP Apparatus II (paddle)
Agitation:	
Medium:	0.1 N HCL, 900 mL, 37 ± 0.5°C
Specification:	

Response: As recommended, we accept the proposed dissolution methodology and specifications. Our analytical controls for Lamictal Chewable Dispersible Tablets will be revised accordingly.

CHEMISTRY, MANUFACTURING, AND CONTROLS

Agency Comment: "The expiration dating period for Lamictal Chewable Dispersible Tablets is 24 months when packaged and stored as per the original NDA submission."

Response: We acknowledge that the expiration dating period for Lamictal Chewable Dispersible Tablets is 24 months and commercial product will be labeled accordingly.

SAFETY UPDATE

Agency Comment: Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDAs by submitting all safety information you now have regarding your new drugs. Please provide updated information as listed below:

1. Submit all safety data including results of trials that were still ongoing at the time of NDA submission. The presentation of this data can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will certainly facilitate review.

2. Submit drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug applications with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the occurrence in the rate of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

Response: Since submission of these applications on September 16, 1996, several updates detailing the safety experience with LAMICTAL Tablets and LAMICTAL Chewable Dispersible Tablets have been provided to the Agency. These include:

- Four Month Safety Update, NDA 20-764, January 17, 1997
- Analysis of Serious Rash Associated with the Use of LAMICTAL in Pediatric Patients, July 22, 1997
- Updated Risk/Benefit Assessment of LAMICTAL and Serious Skin Reactions in Children, August 8, 1997
- Draft Briefing Document prepared for the Peripheral and CNS Drugs Advisory Committee, October 23, 1997

Appended as **Attachment 5** is the Final Safety Update which summarizes the overall safety data for LAMICTAL since submission of the Four Month Safety Update on January 17, 1997 (the subsequent updates only provided analyses and updated information regarding serious rash associated with the use of LAMICTAL in pediatric patients). The cut-off date for the majority of the safety information presented in the initial submission of these applications was 31 December 1995, while that for the Four Month Safety Update was 31 August 1996. Since that time, the original pediatric database for NDA 20-764 (n=399) was expanded to a total of 1071 patients by the inclusion of additional patients exposed to LAMICTAL in pediatric clinical trials that have been completed since submission of the Four Month Safety Update. The Final Safety Update provides updated information for all adverse events between the cut-off date of the last safety update (31 August 1996) and October 31, 1997, with the exception of a cut-off date of 21 November 1997 to accommodate the final results Protocol US 40, a double-blind, placebo-controlled study evaluating adjunctive therapy with LAMICTAL in pediatric patients with partial seizures..

Because of the considerable increase in the size of the safety database for pediatric patients, pertinent sections of the Integrated Summary of Safety Information (ISS) submitted with NDA 20-764 have been updated with new information, including patient

accountability, patient demographics, dosing and extent of exposure, adverse experiences, SAEs, deaths, and withdrawals due to adverse events in pediatric clinical trials completed during this reporting period. The July 22, 1997 amendment to these applications provided an analysis of rash associated with LAMICTAL using a cut-off date of 31 December 1996. Therefore, only-rash-related events reported from 1 January 1997 to 31 October 1997 are summarized in this report. Also included are spontaneous reports of serious adverse events in pediatric patients receiving LAMICTAL as well as a bibliography of published literature from September 1, 1996 to October 31, 1997.

The safety information provided regarding the use of LAMICTAL in adults with epilepsy and/or other indications is limited to new information obtained since submission of the Four Month Safety Update for NDA 20-764 (17 January 1997) and the submission of the sNDA to NDA 20-241 seeking approval of LAMICTAL as monotherapy in adults with partial seizures (24 February 1997). This section includes updated information regarding deaths, serious adverse experiences, and withdrawals due to adverse experiences from ongoing clinical trials as well as spontaneous reports and published literature.

As per previous agreement with the Agency, case report forms for deaths and withdrawals due to adverse experiences are being provided only for completed studies.

Desk copies of the Final Safety Update are being provided to Dr. Feeney and Greg Burkhart, M.D., Team Leader, Safety, under separate cover.

PROMOTIONAL MATERIAL

Agency Comment: "In addition, please submit three copies of the introductory promotional material that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print."

Response: Introductory promotional materials are currently under development and are not yet available. However, it is our understanding from discussions with DDMAC that FDA review of promotional materials prior to use is optional. As required by regulation, all promotional pieces will be filed to the NDA via Form FDA 2253 at the time of initial dissemination.

We trust that this response to the Agency's approvable letter is complete and will allow the Agency to complete the assessment of the application and approve the LAMICTAL Chewable Dispersible Tablets NDA. If there are any questions regarding this submission, particularly the proposed revisions to the package insert, we believe that a brief

teleconference to discuss these questions would be the most expeditious means of resolving these remaining issues. I may be contacted at 919-483-6466 to discuss any aspects of this submission.

We look forward to working with the Agency to finalize the approval of LAMICTAL Chewable Dispersible Tablets and believe that this will be a significant addition to the treatment options available for patients with epilepsy.

Sincerely,

Elizabeth McConnell

APPEARS THIS WAY
ON ORIGINAL

Elizabeth A. McConnell, Pharm.D.
Project Director
Regulatory Affairs

cc: John Feeney, M.D., Reviewing Medical Officer, HFD-120 (Labeling and Final Safety Update)
Greg Burkhart, M.D., Team Leader, Safety, HFD-120 (Final Safety Update)
Jacqueline Ware, Pharm.D., Regulatory Management Officer, HFD-120 (Labeling)

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT 2

1. Executive Summary

- As part of Glaxo Wellcome's ongoing rash risk reduction strategy for lamotrigine (LTG), the company has undertaken various initiatives to learn more about the risk factors for rash.

- As part of these initiatives a previously reported pharmacokinetic (PK) model, now validated using plasma concentrations collected from clinical trials, was used to examine the currently recommended dosing schedules in pediatrics.

- The results of this PK model indicate that the currently recommended LTG dose regimens for children may produce plasma concentrations, during the initial weeks of treatment, which exceed the plasma concentrations produced by the currently recommended dose regimens in adults during the same treatment period. The magnitude of this difference is greatest for pediatric patients on concomitant enzyme inducer AEDs (EIAEDs), although it is also seen in the valproate (VPA) group.

- As a result of these findings and in view of Glaxo Wellcome's position that concomitant use of VPA, LTG starting dose and dose escalation rate are risk factors for rash, the Company is proposing to modify the starting and escalation doses of the pediatric regimen (age 2-12). The LTG maintenance dose ranges are not being amended.

- There is no new clinical and post-marketing safety information suggesting an increased risk of rash in children, or that there are any new risk factors.

- The proposed changes in the starting dose and dose escalation for pediatric patients are based on confirmation of the PK characteristics of LTG in children taking concomitant antiepileptic therapy.

2. Background to adult and pediatric dosing

2.1 Adults

In 1990 LTG was first marketed in Ireland for the treatment of adults with epilepsy. Based on the results of clinical trials and spontaneous post-marketing reports, Glaxo Wellcome developed the position that concomitant VPA, exceeding LTG starting dose and rate of LTG dose escalation were risk factors for the development of rash and rash resulting in the withdrawal of LTG treatment. In 1993 Glaxo Wellcome made the decision to lower the LTG starting dose recommendation in an attempt to decrease the incidence of rash, rash leading to withdrawal, and serious rash. Starting doses for adult patients treated with concomitant VPA were lowered from 50 mg/day to 25 mg on alternate days in Weeks 1&2. At the same time, the LTG starting dose for patients taking EIAEDs was also reduced from 50 mg twice daily to 50 mg once a day for Weeks 1&2 in order to produce initial LTG plasma concentrations that were similar to the levels produced by the revised VPA dose recommendation. Table 1 summarises the current labelled adult doses

Table 1. Current Labelled Adult Doses

	WEEKS 1 & 2	WEEKS 3 & 4
VPA ± AEDs	12.5 mg (given as 25 mg on alternate days)	25 mg (once a day)
EIAEDs ± AEDs except VPA	50 mg (once a day)	100 mg (two divided doses)

2.2 Pediatric

Lamotrigine dosing guidelines for pediatric patients were originally based on a meta-analysis of plasma concentration data obtained from a series of open-label pediatric studies (UK 73, 98, and 102; N = 202 < 18 years of age). The PK model developed from these open data was used to predict doses needed in pediatric patients to achieve average steady-state serum levels of LTG of 4.0 µg/mL. The PK model was not used to simulate different initial doses and dose titrations to achieve maintenance doses. Rather, the initial recommendations for dosing of LTG in pediatric patients utilized dose escalations similar to those used in the open-label protocols on which the model was based.

During pediatric trials an increased incidence of rash (including serious rash) was noted among patients taking LTG with VPA. In an attempt to reduce the incidence, the dose for pediatric patients taking VPA in any combination with other AEDs during clinical trials was reduced by 60% for weeks 1 & 2 and by 50% for weeks 3 & 4. The dosing regimen for patients taking concomitant EIAEDs was not altered. Table 2 below summarises the current labelled pediatric doses of LTG in countries where LTG is approved for pediatric patients (first approval in the UK February 1994).

Table 2. Current Labelled Pediatric Doses

	WEEKS 1& 2	WEEKS 3 & 4
EIAEDs ± AEDs except VPA (mg/kg)	2 mg/kg	5 mg/kg
VPA ± AEDs (mg/kg)	0.2 mg/kg	0.5 mg/kg

3. Re-evaluation of pediatric dosing recommendations on the basis of the validated PK model

The PK basis for pediatric dosing was originally established in a meta-analysis. A population PK model was developed using 652 plasma concentrations obtained from 202 patients enrolled in three open pediatric studies (UK73, UK98 and UK102). The dosage regimens used in these studies were not always the same as the current proposed recommendations. The main assumptions for the model were 1) LTG follows one compartment open model with first order absorption and first order elimination; and 2) LTG PK is linear with dose. These assumptions have been proven valid in adults. There is no evidence to suggest differently in children. The PK model showed that oral clearance of LTG in children was a function of body weight and the concomitant AED. This was consistent with the findings in adults.

The PK model has recently been validated using a further 508 plasma concentrations collected from 148 patients with a mean age of 8 years (ranging 0 to 25 years) enrolled in 4 additional pediatric studies some of which were controlled (UK123, US40, UK61 and PC9001). The technical report of the model validation is attached to this document (see Appendix 3). Eighty-six, 39 and 23 patients in the validation dataset received EIAEDs, VPA or both, respectively. The weight distribution of these patients can be found in Figure 2 of the attached report for the model validation. The results of the validation confirmed the original findings revealed by the model.

The model parameters have been refined using the total of 1160 (652+508) concentrations obtained from the 350 (202+148) patients and used to estimate the plasma concentrations following the current dosage recommendations. The estimated plasma concentrations during the initial 5 weeks of dosage escalation and during an extended period of escalation in patients receiving EIAEDs without VPA following the current recommendations are shown in Appendix 2,

Figures 1 and 2, respectively. The corresponding concentrations in patients receiving VPA without EIAEDs following the current recommendations are depicted in Figures 3 and 4. The projected adult plasma levels are for a 70 kg adult taking the currently recommended adult doses (see table above).

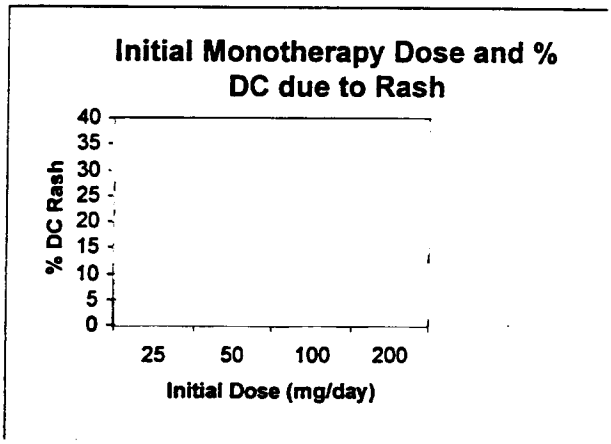
The same dosage is recommended for the patients receiving VPA with or without EIAEDs. Since the clearance in patients receiving LTG and VPA alone is lower than in those receiving LTG and VPA with EIAEDs, the LTG plasma concentrations in the latter group should be lower than those in the former group. There should not be additional concerns with respect to excess doses in-patients concomitantly receiving LTG and VPA with EIAEDS. Therefore our recommendation from the PK model concentrate on the plasma level predictions in patients receiving LTG and VPA without EIAEDs.

The model (Figures 1 to 4) shows that the currently recommended LTG dose regimens for children may produce, on average, plasma concentrations which considerably exceed (in some cases to an extent of 3 to 4-fold) the plasma concentrations produced by the recommended regimens in adults during the initial weeks of treatment. The magnitude of this difference is greatest for pediatric patients on concomitant EIAEDs, although it is also seen in the VPA group. The difference is greater in the heavier children than in the lighter children.

4. Summary of pediatric safety data relating to rash.

4.1 Background

Exceeding the recommended starting dose or rate of dose escalation of LTG in the early weeks of treatment are well established risk factors leading to an increased incidence of non-serious rash as well as rash leading to discontinuation of LTG (see figure below). Concomitant use of VPA is also a well recognized risk factor for rash.



The incidence of rash leading to discontinuation in all adult monotherapy trials as a function of LAMICTAL starting dose.

The relationship between dosing and serious rash is less well established primarily due to the low incidence of serious rash. The relatively few cases of serious rash in the LTG clinical trial database do not allow confirmation of the risk factors for serious rash.

The strongest evidence in support of an effect of dosing on the incidence of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (SJS/TEN) with LTG is the experience in Germany

where a registry for cutaneous reactions to drugs has been established since 1990. This academically based registry, structured as an intensive reporting system, regularly contacts more than 1500 departments including 100% of burn units, departments of pediatrics, departments of dermatology, and all internal medicine departments in hospitals with intensive care facilities or more than 200 beds. Because of the prospective review of potential cases in this registry, these are confirmed cases of SJS or TEN. The registry has been operating continuously since 1990, well in advance of the marketing of LTG in Germany. In the first year of LTG marketing (1993) in Germany there were five LTG related SJS/TEN cases reported, all of whom were also taking VPA, in an estimated 1,270 new patients exposed. In the third quarter of 1993, Glaxo Wellcome amended the dosing regimen and initiated a campaign to inform physicians of the risks associated with excessively rapid LTG dose escalations. The starting dose of LTG when used with VPA was empirically reduced by a factor of four, from 50 mg/day to 25 mg on alternate days, in this amendment. In each of the subsequent two years (1994 with an estimated 15,500 new patients exposed, and 1995 with an estimated 34,700 new patients exposed), two SJS/TEN cases were registered. In 1996, despite continued increased use of LTG, no cases of SJS or TEN have been detected by the registry in patients taking LTG. The rate of SJS/TEN decreased with the implementation of the amended (reduced) dosing schedule. These data provide circumstantial evidence that reduced initial dosing and slower rates of dose escalation can reduce the rate of SJS associated with LTG use.

4.2 Clinical Trial Database

There are two current sources for clinical trial data regarding rash with LTG in adults and pediatric patients: a recently published update of the adult safety database (Drug Safety 1998;18:281-296 ref. 1) and the pediatric rash assessment documents submitted for review to the CPMP Pharmacovigilance Working Party and the FDA in July 1997. Since preparation of these reports there has been no significant new information regarding the incidence of rash with LTG. The data from these sources are summarised in table 3 below.

Table 3. Serious Rash Associated with Hospitalization or reported as possible SJS – Clinical Trials

	EIAEDs	Any VPA	All AEDs combined	Cases of possible SJS
Adults[1]	2/2240 (0.1%)	5/508 (1%)	11/3985 (0.3%)	4/3985 (0.1%)
Pediatric[2]	-	-	11[4]/967 (1.1%)	7/967 (0.7%)
Pediatric[3]	3/401 (0.7%)	4/456 (0.9%)	9[4]/1073 (0.8%)	5/1073 (0.5%)

1 Published report of safety with LTG in adult patients (Drug Safety 1998;18:281-296)
2 Data from documents submitted to CPMP Pharmacovigilance Working Party (copy of report submitted to FDA on 8 August 1997)
3 Data from amendment submitted to FDA (22 July 1997)
4 Data presented in the MCA and FDA documents used different methodologies and therefore the number of cases presented are different and referred to different pediatric categories (2-12 years vs. 2-16 years). The differences are explained in a memo sent to the FDA on 8 August 1997.
Note: in many of these cases the doses were higher than those currently recommended

There is an overall higher incidence of serious rash requiring hospitalization in pediatric (1:100) vs. adult (1:300) patients. Although the size of the clinical trials is limited, it can be noted that the higher incidence of serious rash in pediatric patients is due to an increased incidence of serious rash relative to adults in patients taking concomitant AEDs other than VPA. It should be noted that all three pediatric patients who developed serious rash while taking concomitant EIAEDs received starting doses of LTG within the current dosage guidelines (1.5 - 2 mg/Kg/day).

The pediatric clinical trial database was also examined to determine if there was a relationship between patient weight and the incidence of discontinuation due to rash (Table 4). No trends were evident in this analysis. It should be noted that this analysis is confounded by the fact that clinical trial patients received a variety of starting doses and dose escalations of LTG. However in most cases the clinical trials regimens exceeded current recommendations.

Table 4. Incidence (%) of Discontinuation Due to Rash by Concomitant AED and by Body Weight

	<15 Kg	15-<25 Kg	25-<35 Kg	35-<45 Kg	45-<55 Kg	55-<65 Kg	65-<75 Kg	>=75 Kg
All AEDs	4/99 (4%)	21/400 (5.3%)	12/280 (4.3%)	7/159 (4.4%)	3/72 (4.2%)	0/44	0/16	4/21 (19.1%)
EIAEDs	2/34 (5.9%)	7/142 (4.9%)	2/89 (2.3%)	1/60 (1.7%)	2/32 (6.3%)	0/17 (0%)	0/6 (0%)	2/10 (20%)
VPA+NEI	0/12 (0%)	5/56 (8.9%)	7/42 (16.7%)	2/19 (10.5%)	0/7 (0%)	0/6 (0%)	0/3 (0%)	1/3 (33.3%)
VPA only	1/11 (9.1%)	6/56 (10.7%)	2/38 (5.3%)	1/21 (4.8%)	1/9 (11.1%)	0/4 (0%)	0/1 (0%)	1/3 (33.3%)

To follow-up on the suggestion that patient weight and not patient age contributes most significantly to the PK model, a similar analysis, to determine if there was a relationship between patient weight and the incidence of discontinuation due to rash, was also performed for adults in the adult clinical trials database. Again there was no clear evidence of a trend towards a greater number of discontinuations due to rash in the lower weight adults who had all received fixed mg doses of LTG greater than or equal to our currently labelled dosage recommendations.

4.3 Post-Marketing Database

The pediatric indication was launched in the UK in the second half of 1994. Since then, LTG has been approved for use in pediatric patients as add-on therapy in over 40 countries world-wide. Further information about the relationship between dosing and the risk of serious skin reactions can be gathered from the analysis of all the post-marketing reports of serious skin reactions in children received by Glaxo Wellcome.

Up to 15 May 1998, Glaxo Wellcome had received a total of 4,102 post-marketing reports of suspected adverse reactions to LTG (including spontaneous reports and cases from post-marketing surveillance studies and named-patient use). Of these, approximately 16% concerned children aged 12 years and below. Among these children, a total of 135 serious skin reactions[1] were reported. Sixty-seven of these were reported to have SJS or TEN (or possible SJS/TEN). A detailed analysis of the dose regimen prescribed in these 135 cases has been undertaken and is provided in Table 1 of Appendix 1, together with an explanation of how the data have been calculated. These data are summarised in Table 5.

1. For the purpose of this analysis, any case which met the following criteria was considered to be serious:
   - Cases reported as possible SJS or TEN (whether or not there was evidence to support the diagnosis).
   - Any skin reaction considered by the reporter to be life-threatening, disabling, fatal, or medically serious, or which required hospitalization, treatment with steroids or other significant medical intervention.

Table 5. Dose regimen prescribed for all world-wide serious skin reactions reported in children between launch and 15 May 1998

Concomitant medication	Dose regimen prescribed compared with current dosage recommendations (number of patients)			Total
	> Recommended	As Recommended	Unknown	
Concurrent VPA (± other AEDs)	64	12	15	**91**
Concurrent EIAEDs (no VPA)	2	5	2	**9**
Concurrent non-EIAEDs (no VPA)	10	3	1	**14**
Monotherapy	5	0	2	**7**
Unknown	4	1	9	**14**
Totals	**85**	**21**	**29**	**135**

The following information is apparent from this analysis:

- Information on the concurrent medication taken is lacking in 14 (10%) cases
- Of the patients in whom concurrent medication was specified (n=121), 91 (75%) were known to be on VPA, 14 (12%) were on non-EIAEDs, 9 (7%) were on EIAEDs and 7 (6%) were on LTG monotherapy.
- Information on the dose regimen prescribed was lacking in 29 (27%) of cases, but is available for the other 106 cases.
- Out of the 106 cases, 85 (80%) episodes occurred in children who received higher doses of LTG than currently recommended (either in terms of the initial dose or the rate of dose escalation), while 21 episodes (20%) occurred in children who were dosed in accordance with the current recommendations.
- Most of the children on VPA received higher doses than currently recommended (64 out of 76 cases where information on dose was available; 84%), however, 12 cases (16%) occurred in children receiving the currently recommended dose.
- For children on EIAEDs, the majority of episodes (5 out of 7 cases) occurred in children who were dosed in accordance with the current recommendations, although the total number of cases in the enzyme-inducing group was small.

It is clear that the majority of serious skin reactions (91/121; 75%) reported in the post-marketing period have occurred in children taking VPA concurrently. A relatively small proportion of patients (9/121, 7%) were taking concurrent enzyme-inducing drugs, but no VPA. Although most cases have occurred in children who have received doses of LTG in excess of that currently recommended, it is apparent that serious rash also occurs at the currently recommended doses. However, no new risk factors have emerged from review of these data.

5. Recommendation for Revised Pediatric Dosing

According to the results from the PK analyses and simulations (figures 1 to 4), the difference in estimated plasma concentrations in children compared to adults is greater in those pediatric patients receiving EIAEDs than in those receiving VPA. Based on previous clinical trial experience from adults and children, lower starting dose recommendations in children would be

expected to further lower the rate of non-serious rash, and may also lower the incidence of serious rash. Efforts have been made to identify easy-to -implement pediatric dosage regimens that would generate plasma concentrations similar to those predicted in adults while minimising the risk of the delay in the onset of efficacy.
The estimated plasma concentrations from new pediatric dosing regimens are presented in Figures 5 to 8.

The new proposed pediatric dosing regimen are presented in Table 6 below.

first two weeks

If the calculated daily dose is less than 2.5 mg, then LTG should not be administered..

6 Conclusions

- Exceeding the recommended starting dose or rate of dose escalation of LTG in the early weeks of treatment are well established risk factors leading to an increased incidence of non-serious rash as well as rash leading to discontinuation of LTG. Concomitant use of VPA is also a well recognized risk factor for rash.

- The relationship between dosing and serious rash is less well established primarily due to the low incidence of serious rash. The relatively few cases of serious rash in the LTG clinical trial database do not allow confirmation of dosing as a risk factor for serious rash.

- There is no new clinical and post-marketing safety information on the risk of rash in children and no new risk factors have been identified.

- The results of the PK model indicate that the currently recommended LTG dose regimens for children may produce plasma concentrations, during the initial weeks of treatment, which exceed the plasma concentrations produced by the currently recommended dose regimens in adults during the same treatment period. The magnitude of this difference is greatest for pediatric patients on concomitant enzyme inducer AEDs (EIAEDs), although it is also seen in the valproate (VPA) group.

- As a result of these findings and in view of Glaxo Wellcome's position that concomitant use of VPA, LTG starting dose and dose escalation rate are risk factors for rash, the Company is proposing to modify the starting and escalation doses of the pediatric regimen (age 2-12). The LTG maintenance dose ranges are not being amended.

- The proposed changes in the starting dose and dose escalation for pediatric patients are based on the confirmation of the PK characteristics of LTG in children taking concomitant antiepileptic therapy.

APPENDIX 2:

Figures of Estimated Average Plasma Concentrations of Lamotrigine during the Initial 5 Weeks of Dose Escalation

Figure 1. Estimated Average Plasma Concentrations during the Initial 5 Weeks of Dose Escalation Following the Current Dose Recommendations in Patients Receiving EIAED

Adults: weeks 1 and 2: 50mg/day; weeks 3 and 4: 100mg/day; weekly increment: 100mg/day.

Children: weeks 1 and 2: 2mg/kg; weeks 3 and 4: 5mg/kg/day; weekly increment: 2.5mg/kg/day.

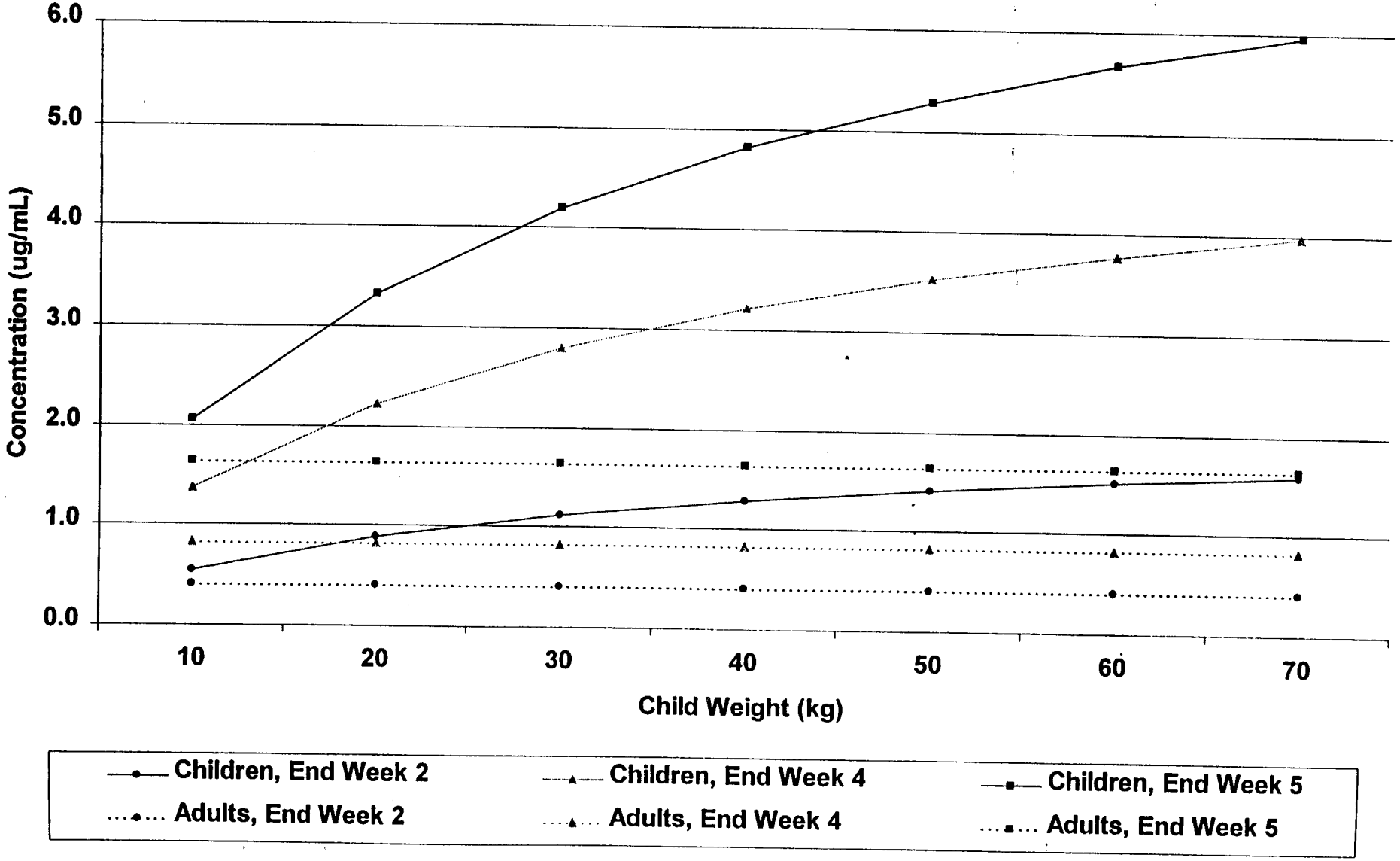


Figure 2. Estimated Average Plasma Concentrations during an Extended Period of Dose Escalation Following the Current Dose Recommendations in Patients Receiving EIAED

Adults: weeks 1 and 2: 50mg/day; weeks 3 and 4: 100mg/day; weekly increment: 100mg/day.

Children: weeks 1 and 2: 2mg/kg; weeks 3 and 4: 5mg/kg/day; weekly increment: 2.5mg/kg/day.

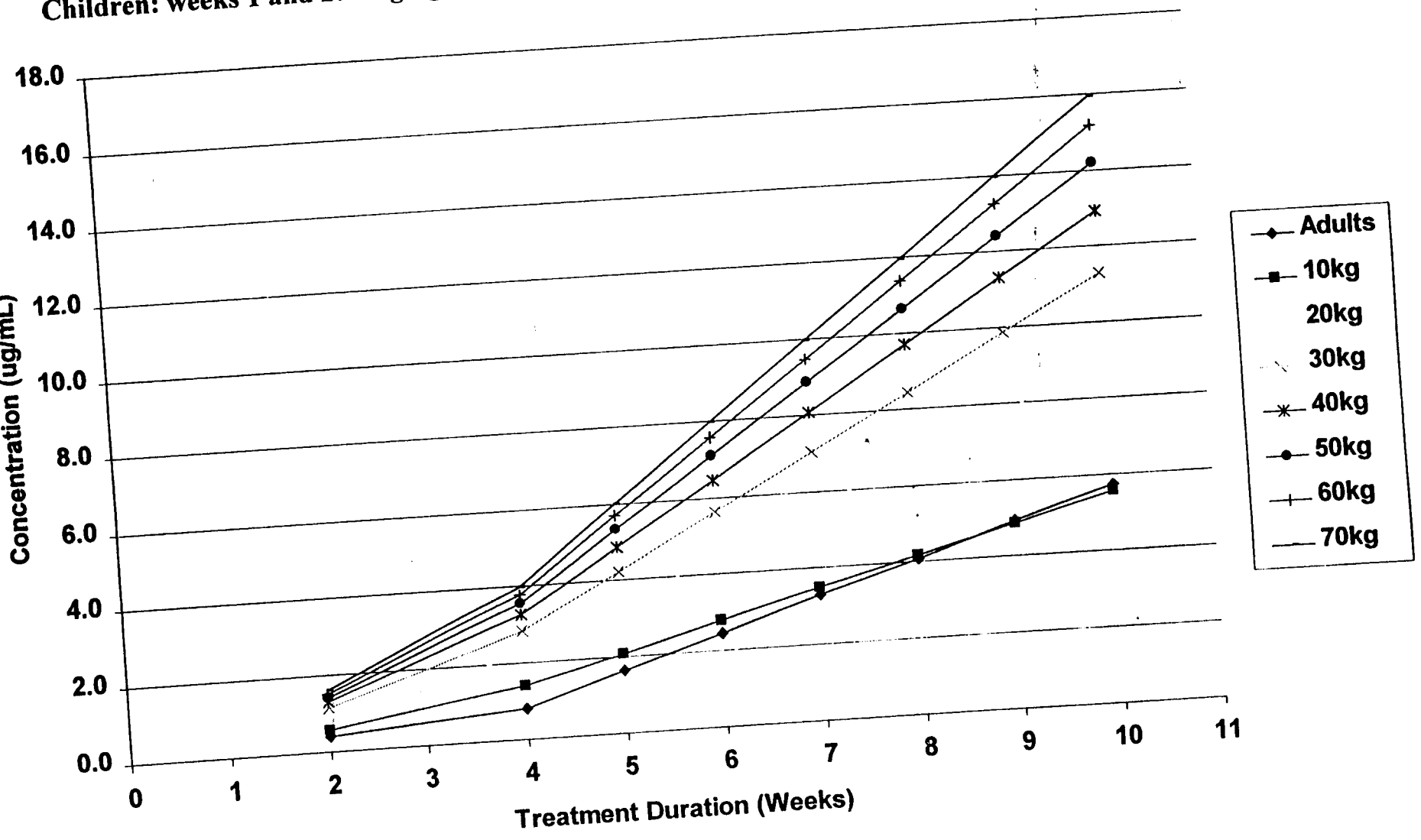


Figure 3. Estimated Average Plasma Concentrations during the Initial 5 Weeks of Dose Escalation Following the Current Dose Recommendations in Patients Receiving VPA

Adults: weeks 1 and 2: 12.5mg/day; weeks 3 and 4: 25mg/day; weekly increment: 25mg/day.

Children: weeks 1 and 2: 0.2mg/kg; weeks 3 and 4: 0.5mg/kg/day; weekly increment: 0.5mg/kg/day.

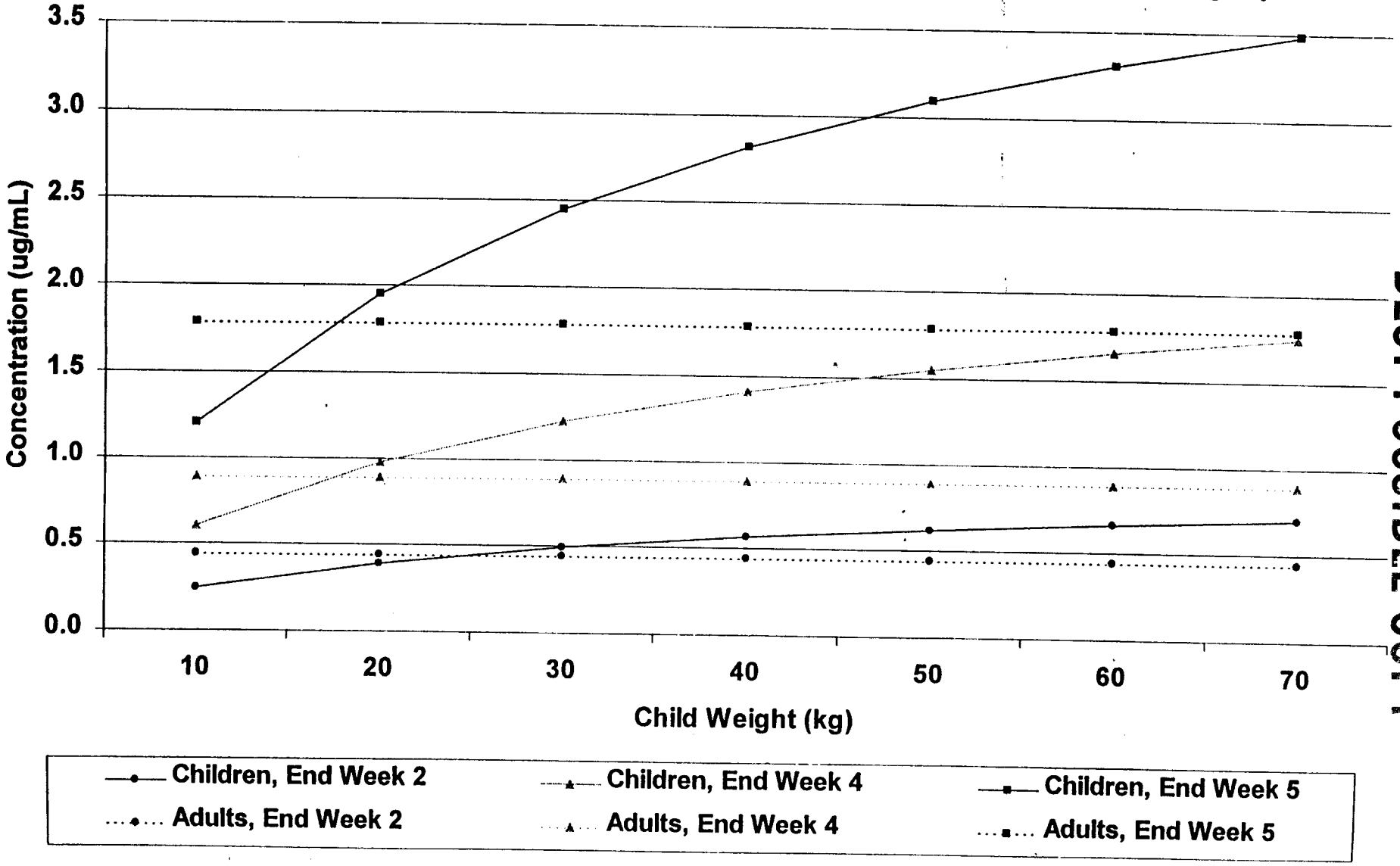


Figure 4. Estimated Average Plasma Concentrations during an Extended Period of Dose Escalation Following the Current Dose Recommendations in Patients Receiving VPA

Adults: weeks 1 and 2: 12.5mg/day; weeks 3 and 4: 25mg/day; weekly increment: 25mg/day.

Children: weeks 1 and 2: 0.2mg/kg; weeks 3 and 4: 0.5mg/kg/day; weekly increment: 0.5mg/kg/day.

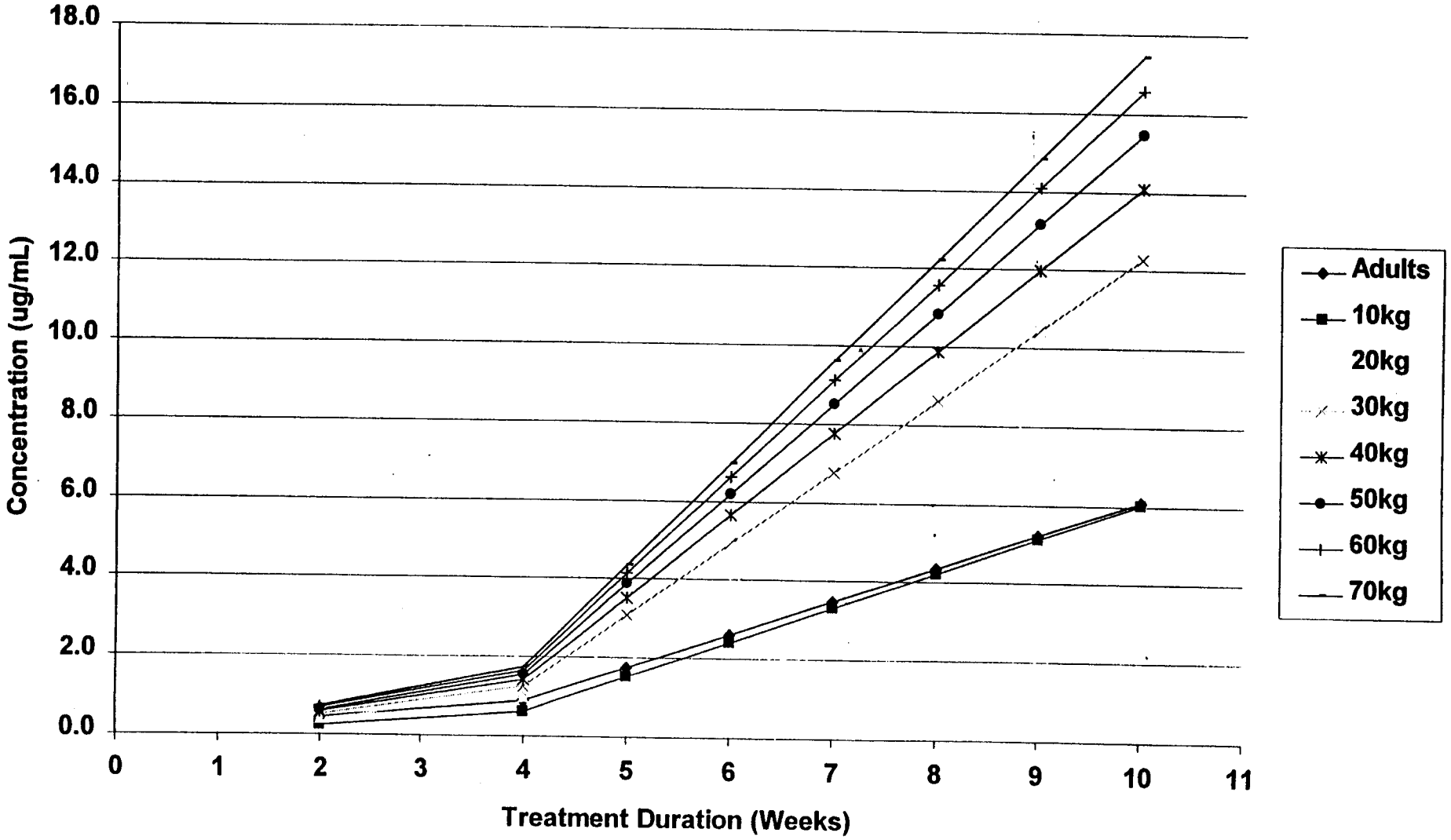


Figure 5. Estimated Average Plasma Concentrations during the Initial 5 Weeks of Dose Escalation Following the Proposed Dose Recommendations in Patients Receiving EIAED

Adults: weeks 1 and 2: 50mg/day; weeks 3 and 4: 100mg/day; weekly increment: 100mg/day.

Children: weeks 1 and 2: 0.6mg/kg; weeks 3 and 4: 0.6mg/kg/day; weekly increment: 1.2mg/kg/day.

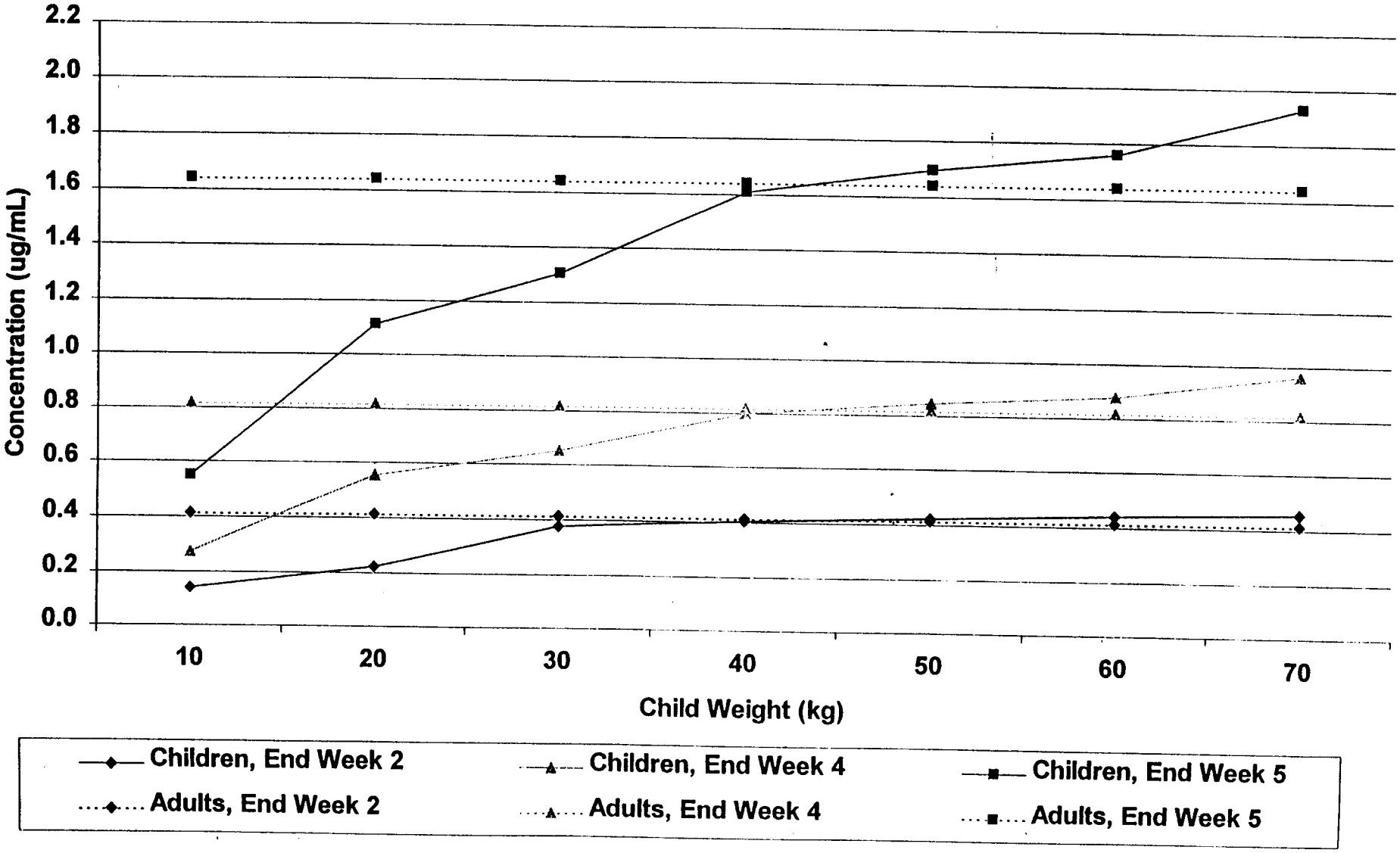


Figure 6. Estimated Average Plasma Concentrations during an Extended Period of Dose Escalation Following the Proposed Dose Recommendations in Patients Receiving EIAED

Adults: weeks 1 and 2: 50mg/day; weeks 3 and 4: 100mg/day; weekly increment: 100mg/day.

Children: weeks 1 and 2: 0.6mg/kg; weeks 3 and 4: 0.6mg/kg/day; weekly increment: 1.2mg/kg/day.

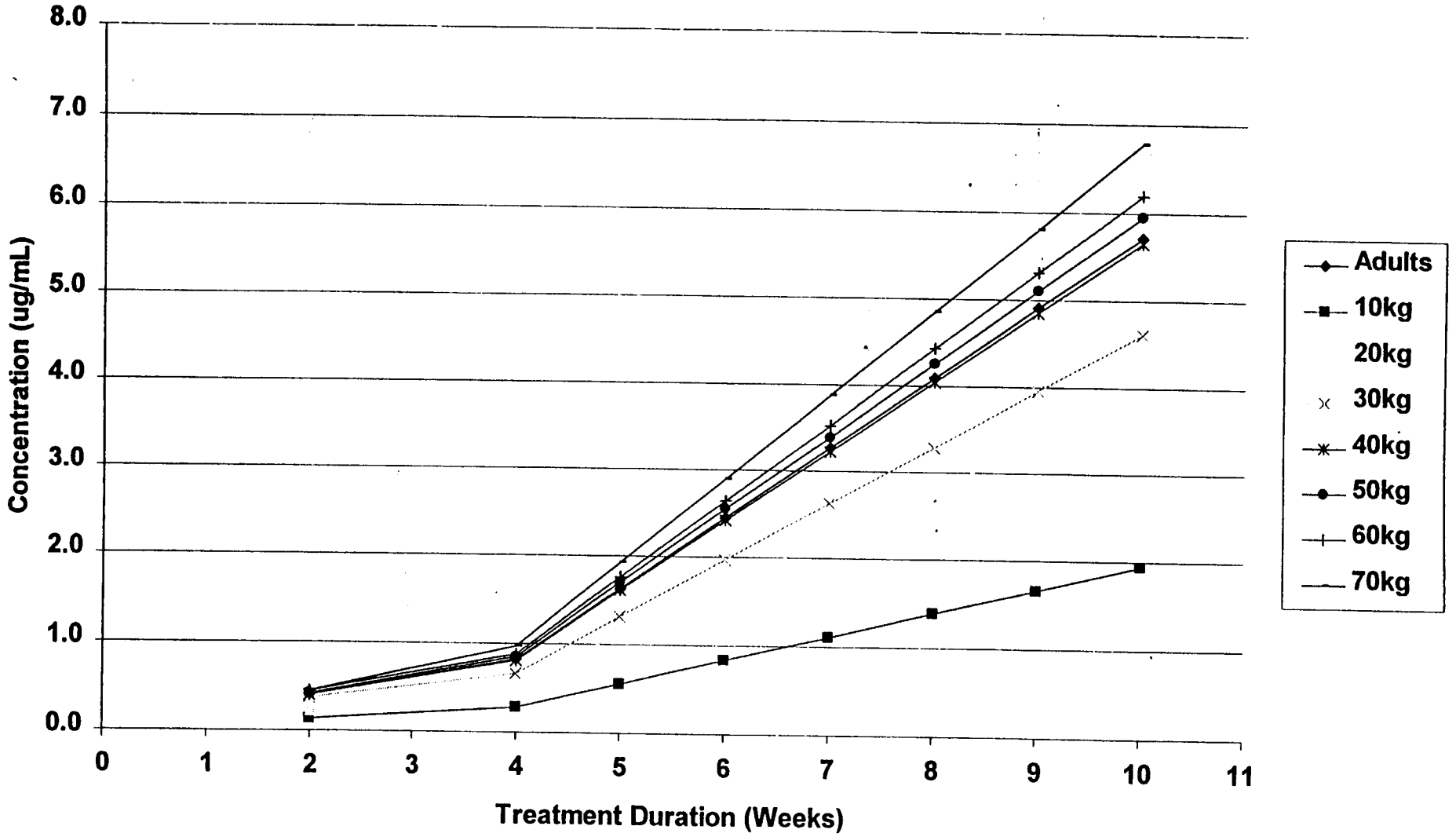


Figure 7. Estimated Average Plasma Concentrations during the Initial 5 Weeks of Dose Escalation Following the Proposed Dose Recommendations in Patients Receiving VPA

Adults: weeks 1 and 2: 12.5mg/day; weeks 3 and 4: 25mg/day; weekly increment: 25mg/day.

Children: weeks 1 and 2: 0.15mg/kg; weeks 3 and 4: 0.3mg/kg/day; weekly increment: 0.3mg/kg/day.

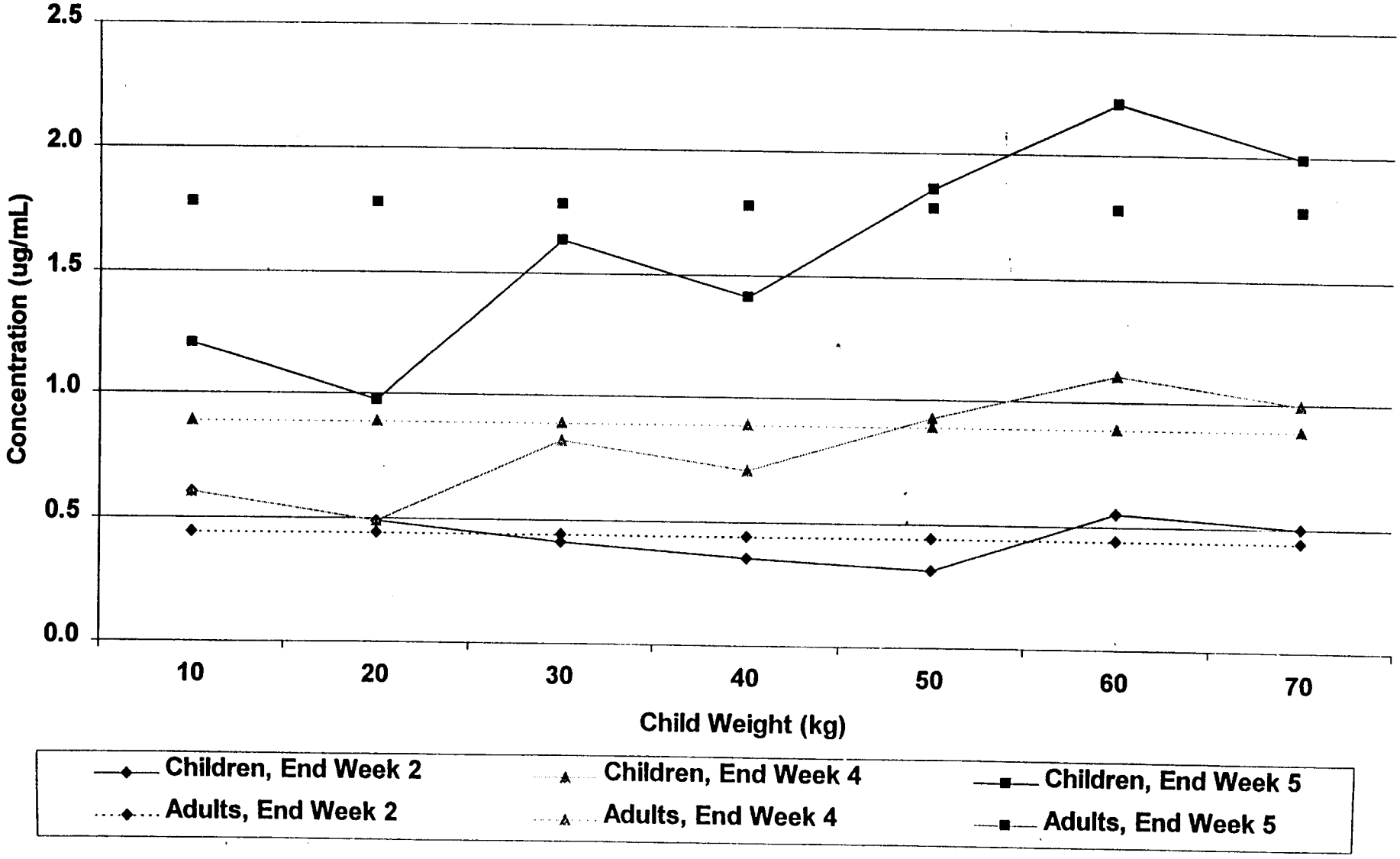


Figure 8. Estimated Average Plasma Concentrations during an Extended Period of Dose Escalation Following the Proposed Dose Recommendations in Patients Receiving VPA

Adults: weeks 1 and 2: 12.5mg/day; weeks 3 and 4: 25mg/day; weekly increment: 25mg/day.

Children: weeks 1 and 2: 0.15mg/kg; weeks 3 and 4: 0.3mg/kg/day; weekly increment: 0.3mg/kg/day.