Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

Gabapentin

Neurontin

PT/W/0001/pdWS/001

Rapporteur:	**Portugal (PT)**
Finalisation procedure (day 120):	**30-12-2011**

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Neurontin
INN (or common name) of the active substance(s):	Gabapentin
MAH (s):	Pfizer Ltd.
Pharmaco-therapeutic group (ATC Code):	N03AX12
Pharmaceutical form(s) and strength(s):	100, 300, and 400 mg capsules, hard 600 and 800 mg tablets, film coated

I. EXECUTIVE SUMMARY

The active substance is gabapentin.
SmPC changes are proposed in section 5.2.

Summary of outcome

☐ No change

☒ Change

☒ New study data: in section 5.2

II. RECOMMENDATION

Based on the data submitted, SmPC changes are proposed in section 5.2.

Gabapentin pharmacokinetics in children were determined in 50 healthy subjects between the ages of 1 month and 12 years. In general, plasma gabapentin concentrations in children > 5 years of age are similar to those in adults when dosed on a mg/kg basis.

We propose to add:

In a pharmacokinetic study in 24 healthy paediatric subjects aged between 1 month and 48 months, an approximately 30% lower exposure (AUC), lower Cmax **and higher** clearance per body weight have been observed in comparison to available reported data in children older than 5 years.

The applicant is requested to submit a Type IB variation to update the SmPC in line with the above work-sharing recommendations by 01.03.2012, if not already included.

III. INTRODUCTION

The MAH Pfizer submitted 13 completed paediatric studies for gabapentin in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Neurontin and that there is no consequential regulatory action.

In addition, the following documentation has been included as per the procedural guidance:

- A line listing

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

In the submitted studies the pharmaceutical formulations used were:
Gabapentin capsules 100 mg, 200 mg, 300 mg and 400 mg;
Gabapentin oral solution 50 mg/ml
Gabapentin oral solution 20-mg/ml

Assessor's comment:
In EU only the gabapentin capsules 100 mg, 200 mg and 400 mg are approved. We do not believe that is possible to administrate the gabapentin capsules to all paediatric patients, because some of them will have swallowing difficulties of solid dosage formulations. However, there is no information about the conditions for extemporaneous formulation.

According to the MAH, a gabapentin oral solution has been marketed in the United States since March 2000. An abridged application was submitted to BfArM in 2008, to seek approval for gabapentin oral solution on the basis of its bioequivalence with the gabapentin capsule formulation.

IV.2 Non-clinical aspects

1. Introduction

The MAH hasn't submitted non-clinical studies.

IV.3 Clinical aspects

1. Introduction

Gabapentin has been marketed in Europe since May 1993. In the European Union (EU), gabapentin is available in 100 mg, 300 mg, and 400 mg capsules and in 600 mg and 800 mg tablets. Gabapentin oral solution has been marketed in the United States since March 2000.

Gabapentin is indicated in the EU for the treatment of:

Epilepsy

Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and children aged 6 years and above.

Gabapentin is indicated as monotherapy in the treatment of partial seizures with and without secondary generalization in adults and adolescents aged 12 years and above.

Treatment of peripheral neuropathic pain

Gabapentin is indicated for the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults.

The MAH submitted information about:

1. Pharmacokinetics studies

- Study 945-202 Single dose study of gabapentin PK in healthy paediatric subjects (report)
- Study 945-296 Single-dose PK study in healthy infants and children (protocol)

2. Adjunctive therapy studies

- Study 945-86/186 A 12-Week, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study of Gabapentin as Add-On Therapy in Children With Refractory Partial Seizures (report)
- Study 945-87/187 Open-Label Extension of a Double-Blind, Placebo-Controlled, Multicenter Study of Gabapentin (CI-945, Neurontin) as Add-On Therapy in Children With Partial Seizures (report)
- Study 945-305/405 A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study in Paediatric Patients Aged 1 Month to 36 Months With Refractory Partial Seizures (report)
- Study 945-301/401 Open-Label, Safety Study of Gabapentin as Adjunct Therapy in Children Aged 1 Month Through 4 Years With Seizures Uncontrolled by Current Anticonvulsant Drugs (protocol)

3. Monotherapy studies

- Study 945-094 : Gabapentin Paediatric Monotherapy Trial: A Multicenter, Double-Blind, Placebo-Controlled, Parallel-Group Study in Paediatric Patients With Benign Childhood Epilepsy With Centrotemporal Spikes (report)
- Study 945-095 Extended Open-Label Gabapentin (CI-945) Paediatric Monotherapy Trial Following a Double-Blind Study (Protocol 945-094) in Paediatric Patients With Benign Childhood Epilepsy With Centrotemporal Spikes (BECTS) (case report tabulations)

4. Others studies in paediatric populations

- Study 877-034 Open-label extension of an open-label, pilot study of safety and tolerance of gabapentin capsules as add-on therapy in the treatment of juvenile patients with partial seizures (report)
- Studies 945-19/20 Double-blind, placebo-controlled, multicenter studies of the safety and efficacy of gabapentin monotherapy in patients with childhood absence epilepsy naïve to antiepileptic drug therapy (report)
- Studies 945-49/50 Extended-treatment studies of the safety and efficacy of gabapentin monotherapy in patients with childhood absence epilepsy naïve to antiepileptic drug therapy (report)
- Study 945-008 : A Double-Blind, Placebo-Controlled, Multicenter Study, With an Open-Label Extension, of the Safety and Efficacy of Gabapentin as Add-On Therapy in the Treatment of Pharmacotherapy- Resistant Childhood Symptomatic Epilepsies (report)

- Safety and Efficacy of Gabapentin as Add-On Therapy in the Treatment of Pharmacotherapy- Resistant Childhood Symptomatic Epilepsies Study 945-188 Study in healthy volunteers to determine the taste acceptability of 3 gabapentin liquid formulations (report)

The MAH submitted the information of 19 studies that were not paediatric studies but enrolled a small number of patients between 12 and 18 years old. The number of paediatric patient per study is too small, and no separated analysis for de paediatric patients was been made, relative to safety or efficacy.

The MAH submitted a clinical overview that includes a safety review.

2. Clinical studies

Pharmacokinetics studies

Study 945-202
Title: A Single-Dose Study of Neurontin (Gabapentin; CI-945) Pharmacokinetics in Healthy Paediatric Subjects

- **Description**
  - Study 945-202 was an open-label, single dose study in healthy paediatrics subjects. The study, which was conducted at 1 center sites in US, was intended to characterize gabapentin pharmacokinetics in healthy paediatric subjects. Period of study was: 12/09/95 to 12/10/95

- **Methods**

  - Objective(s)
    - To characterize gabapentin pharmacokinetics in healthy paediatric subjects

  - Study design
    - The study was an open-label, single-dose study in healthy paediatric subjects. The subjects were divided into 3 groups based on subject weight. Subjects weighing between 16-25, 26-36, and 37-50 kg received a single AM dose on Day 1 of 200, 300, and 400 mg, respectively, following an 8-hour fast.

  - Study population /Sample size
    - Twenty-four healthy paediatric subjects (17 males and 7 females) completed the study. Seven, 8, and 9 subjects received a single gabapentin capsules dose of 200, 300, and 400 mg, respectively.
    - Healthy male and female paediatric volunteers weighing between 16 to 50 kg.

  - Treatments
    - Single 200-, 300-, or 400-mg gabapentin capsules doses were administered on Study Day 1.

TABLE 2. Dose Groups Based on Body Weight in Protocol 945-202

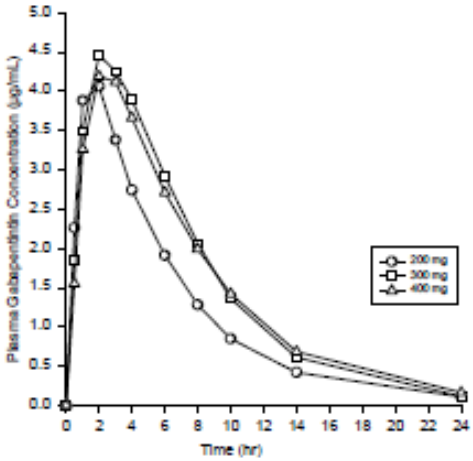
Group	No. of Subjects	Weight Range (kg)	Single AM Dose (mg)
1	8	16-25	200
2	8	26-36	300
3	8	37-50	400

- Outcomes/endpoints
  - Data from all 24 subjects were used in the safety evaluation and in the pharmacokinetic evaluations.
- Statistical Methods
  - Gabapentin pharmacokinetic parameter values were estimated using non compartmental methods. Mean, median, and percent relative standard deviation values were determined for the pharmacokinetic parameters. The relationship between dose (weight) groups and pharmacokinetic parameters was examined by inspection of individual and mean values.

Results

- Recruitment/ Number analysed
  - Twenty-four subjects completed the study. Mean (range) age, weight, and height of the subjects who completed the study were 8.7 (4-12) years, 33.8 (16.4-52.1) kg, and 133.6 (104.8-158.8) cm, respectively.

- **Pharmacokinetics:**
  - Data from all 24 subjects who completed the study were included in the pharmacokinetic and statistical analyses. Mean plasma gabapentin concentration-time profiles for the 3 dose groups are illustrated in the following figure.



Mean (%RSD) pharmacokinetic parameter values from this study are summarized in the following table:

Parameter	Neurontin Dose (mg)					
	200		300		400	
Age Range (yr)	4-6		7-12		8-12	
Weight (kg)	20.5	(13.2)	33.2	(9.3)	44.5	(11.0)
Dose (mg/kg)[a]	9.8	(13.3)	9.1	(9.9)	9.1	(11.0)
Cmax (µg/mL)	4.35	(31.5)	4.55	(25.9)	4.48	(27.5)
tmax (hr)	1.4	(35.7)	2.9	(20.7)	2.7	(37.0)
t½ (hr)	5.40	(16.9)	4.26	(9.9)	4.87	(10.7)
AUC(0-∞) (µg•hr/mL)	28.8	(42.0)	37.7	(17.8)	37.4	(30.7)
Ae%	30.7	(26.4)	48.9	(31.9)	37.0	(28.4)

[a] Dose (mg/kg) based on actual weight of subjects

In general, mean gabapentin pharmacokinetic parameter values observed in the 3 paediatric weight groups were similar. Modest pharmacokinetic differences observed in the smallest weight group can in part be accounted for by the lack of proportionality between body surface area and weight in children, and the fact that gabapentin clearance is proportional to body surface area. Pharmacokinetic parameter values in children were comparable to those in healthy adult subjects who received a similar gabapentin dose based on body weight.

- Safety results

  - There were no serious adverse events reported in this study. There were no withdrawals related to adverse events. Two subjects reported 3 mild adverse events considered possibly related to the single dose of Neurontin. One subject vomited and the other reported being dizzy and tired.

Conclusions: Overall, the pharmacokinetics of gabapentin in adults and children are similar.

Study 945- 269
Title: A Single-Dose Study of Gabapentin Syrup (CI-945) Pharmacokinetics in Healthy Infants and Children

- **Description**
  - Study 945-269 was a non blind, single dose study. This studies, was conducted at one center in US. The objective of this study was to characterize single dose gabapentin pharmacokinetics in healthy infants and children. Studied Period (years): 13/12/98 through 26/02/99.

- **Methods**
  - Objective(s)
    - The objectives of this study were to characterize single-dose gabapentin pharmacokinetics in healthy infants and children.
  - Study design
    - Open-label, single-dose, pharmacokinetic study in healthy paediatric subjects

  - Study population /Sample size
    - Planned enrolment was 24 subjects.

- Treatments
  - Neurontin syrup, 50 mg/mL (Lot CZ-1191097) administered orally in a dose of 10 mg/kg following a 2-hour fast. A single oral dose on Day 1

- Criteria for Inclusion
  - Healthy paediatric subjects were enrolled in 4 age groups (≥1 and ≤3 months; >3 and ≤12 months; >12 and ≤30 months; and, >30 and ≤48 months) to ensure enrolment across a wide range of ages.
- Pharmacokinetic Sampling and Analysis
  - Plasma samples collected serially for 24 hours after each treatment were assayed for gabapentin concentration by a HPLC-UV method validated from 0.02 µg/mL, the lower limit of quantitation, to 5.0 µg/mL.
- Criteria for Evaluation
  - Subjects providing adequate concentration-time data were included in the pharmacokinetic analysis. All subjects were included in the safety analysis.
- Pharmacokinetic and Statistical Analysis
  - Pharmacokinetic parameter values were estimated using standard noncompartmental methods. Descriptive statistics of parameters for each age group were examined for differences of potential clinical importance. Relationships between subject demographics and parameter values were examined to assist in dose recommendations for this group of patients.

- **Results**

- Recruitment/ Number analysed
  - A total of 26 subjects were enrolled and 24 subjects completed this study. Two subjects were withdrawn, 1 for an adverse event (vomiting) and 1 for loss of patent venous catheter. Demographics of the enrolled subjects are summarized by age group in the following table. Following discussions with the FDA, neonates were not included in this study.

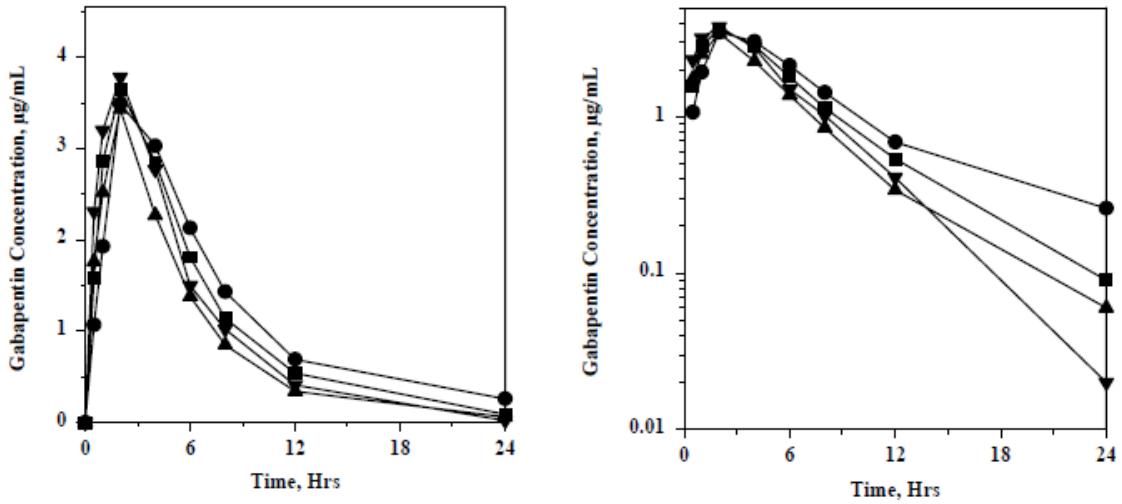
	Age Groups (Months)			
	≥1 and ≤3	>3 and ≤12	>12 and ≤30	>30 and ≤48
n	5	7	9	5
Age (Months)	1.2	7.0	20.0	36.0
Height (cm)	56.0	66.6	83.1	94.3
Weight (kg)	4.9	7.7	11.8	13.9

- Efficacy results
  - Because the minimum number of patients needed for valid analysis of efficacy did not enroll in the study, only safety data were evaluated.

- Safety results

- Overall, single doses of gabapentin syrup were well-tolerated by healthy paediatric subjects ranging in age between 1 to 48 months.

- Pharmacokinetic:
  - Gabapentin plasma concentrations are illustrated in the following figures.



Mean Gabapentin Plasma Concentrations by Age Group are Presented Above; Group 1 (●), ≥1 and ≤3 Months; Group 2 (■), >3 and ≤12 Months; Group 3 (▲), >12 and ≤30 Months; Group 4 (▼), >30 and ≤48 Months

- Pharmacokinetic parameter values are summarized in the following table.

Parameter	Mean Values (%RSD) by Enrollment Age Group			
	≥1 and ≤3 (n = 5)	>3 and ≤12 (n = 7)	>12 and ≤30 (n = 7)	>30 and ≤48 (n = 5)
Age, months	1.20 (37.3)	7.00 (46.7)	18.4 (32.7)	36.0 (19.5)
Weight, kg	4.92 (22.0)	7.81 (19.5)	11.3 (12.9)	13.9 (13.4)
CLcr, mL/min	13.6 (35.8)	27.2 (27.4)	42.7 (20.2)	51.1 (38.8)
Cmax, µg/mL	3.56 (45.1)	3.93 (44.7)	3.43 (23.7)	3.87 (17.8)
tmax, hr	2.80 (39.1)	1.95 (51.6)	2.00 (0)	2.42 (36.4)
AUC(0-tldc), µg·hr/mL	27.1 (33.4)	25.1 (54.8)	20.0 (20.3)	22.9 (20.2)
AUC(0-∞), µg·hr/mL	31.1 (30.6)	26.5 (52.9)	20.9 (20.4)	23.8 (19.0)
t½ hr	5.15 (27.1)	4.75 (46.7)	3.39 (22.2)	2.92 (23.9)
CL/F, mL/min	28.5 (39.2)	57.0 (36.2)	93.3 (21.2)	101 (25.1)
CL/F, mL/min/kg	5.73 (27.2)	7.45 (37.3)	8.33 (24.3)	7.24 (21.8)

- Gabapentin Cmax and AUC values were generally similar across the age range of subjects in this study, indicating exposure to gabapentin was similar among infants and children between 1 and 48 months of age when gabapentin is administered on a milligram/kilogram basis. Values for t½ tended to be slightly longer in younger subjects.

- A linear relationship existed between gabapentin oral clearance and subject CLcr, indicating that CLcr is a good predictor of gabapentin CL/F in children just as it was in adults with various degrees of renal function. Metabolism was not a detectable pathway for gabapentin elimination in children.

CONCLUSION: The pharmacokinetics of gabapentin in children between the ages of 1 and 48 months of age are similar.

Assessor's comment:
According with the data of this study and comparing with the data of the study **945-202** *Single dose study of gabapentin PK in healthy paediatric subjects*, paediatric subjects between 1 month and 48 month achieved approximately 30% lower exposure (AUC) than that observed in those older than 5 years, Cmax is lower and the clearance per body weight is higher in younger children. These data apparently indicate that children < 48 month of age should receive a 30% higher daily dose of gabapentin on a mg/kg basis than children older than 5 years of age in order to achieve comparable drug exposure.

Adjunctive therapy studies

Study 945-86/186
Title: A 12-Week, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study of Gabapentin as Add-On Therapy in Children With Refractory Partial Seizures

- **Description**
  - Study 945-86/186 was a double-blind, placebo-controlled, parallel-group, multicenter study. The study, which was conducted at fifty-four centers in Europe, South Africa, and the United States, was intended to evaluate the safety and efficacy of gabapentin compared with placebo as add-on therapy in the treatment of paediatric patients with medically uncontrolled partial seizures. Studied period (years): 06/06/93 to 20/11/96

- **Methods**
  - Objective(s)
    - To evaluate, under double-blind, placebo-controlled conditions, the safety and efficacy of gabapentin compared with placebo as add-on therapy in the treatment of paediatric patients with medically uncontrolled partial seizures. To compare the global effects of add-on gabapentin versus placebo on patients' seizures and well-being.

  - Study design
    - After screening, patients entered a 6-week baseline period in which current antiepileptic drug (AED) therapy continued. Following baseline, patients entered a 12-week double-blind period where they were randomized to receive either placebo or gabapentin (23.2-35.3 mg/kg/day) as add-on therapy. Current AED therapy was maintained.

  - Study population /Sample size

- A total of 247 patients were randomized to treatment: 119 received gabapentin and 128 received placebo.
- Boys or girls, 12 years of age or younger, with refractory partial seizures, who weighed between 37.5 and 158.9 lb (17-72 kg), were able to swallow capsules, and were currently receiving 1, 2, or 3 standard AEDs. Patients were required to have at least 4 seizures during the 6-week baseline period, with at least 1 in each 2-week period, to continue into the double-blind phase.

- Treatments:
  - Test product: Gabapentin capsules 100mg and 200mg or placebo capsules
  - Administration: Oral, TID, 600, 900, 1200, or 1800 mg/day, to reach a target dosage of 23.2 to 35.3 mg/kg/day
  - Duration of Treatment**:** 12 weeks

TABLE 2. Study Design and Dosing Schedule During the Double-Blind Phase

Weight Range (kg)	Medication Set	Day 1		Day 2		Day 3 and Remainder of Study		
		Total Number of Capsules per Day	Total mg/kg/day	Total Number of Capsules per Day	Total mg/kg/day	Total Number of Capsules per Day	Total mg/kg/day	Total mg/day
17-25.9	A	3	11.6-17.6	3	11.6-17.6	6	23.2-35.3	600
26-36.9	A	3	8.1-11.5	6	16.3-23.1	9	24.4-34.6	900
37-50.9	B	3	11.8-16.2	3	11.8-16.2	6	23.6-32.4	1200
51-72	B	3	8.3-11.8	6	16.7-23.5	9	25.0-35.3	1800

A = 100-mg gabapentin or placebo capsules; B = 200-mg gabapentin or placebo capsules.

- Outcomes/endpoints
  - The primary criterion to establish the efficacy of gabapentin was the reduction in seizure frequency of all partial seizures during treatment as compared with baseline seizure frequency. The primary efficacy variable was Response Ratio (RRatio). RRatio is defined as T – B /T + B, Where: T = Seizure frequency per 28 days during double-blind. B = Seizure frequency per 28 days during baseline.
  - Responder rate was a complementary variable and is defined as the proportion of patients with at least a 50% decrease in seizure frequency from baseline to treatment. Secondary efficacy variables were percent change (PCH) from baseline in partial seizure frequency; RRatio and PCH for individual types of partial seizures; and global assessments by the investigator and the parent/guardian of patient well-being and of seizure frequency. Safety was evaluated using adverse events, serious adverse events, withdrawals due to adverse events, results of clinical laboratory tests, and physical and neurological examinations.

- Statistical Methods
  - The primary efficacy analyses utilized data from a modified intent-to-treat (MITT) population, while the robustness of the results were tested in supplemental analyses of data for the intent-to-treat (ITT) population, which comprised all randomized patients. RRatio was evaluated by analysis of variance (ANOVA). Responder rates were analyzed using the Cochran-Mantel-Haenszel (CMH) test, adjusting for center to test for a treatment difference. All testing was 2-sided, and significant if $p < 0.05$. A 95% confidence interval was provided for the difference between gabapentin and placebo in mean RRatio and median PCH. Descriptive statistics by seizure type were computed for RRatio and PCH. Global assessments

of well-being and seizure frequency by the physician and parent/guardian were compared between the treatment groups using the CMH test.

- **Results**

- Recruitment/ Number analysed
  - A total of 272 patients entered baseline, but since 25 were withdrawn, 247 patients ranging in age from 3 to 12 years entered the double-blind treatment phase.
- Baseline data
  - A total of 272 patients entered baseline, but since 25 were withdrawn, 247 patients ranging in age from 3 to 12 years entered the double-blind treatment phase. Of these, 119 patients (59 boys and 60 girls) with a mean age of 8.5 years [±2.4, standard deviation (SD)] were randomly assigned to the gabapentin treatment group and 128 patients (75 males and 53 females) with a mean age of 8.4 (±2.7) years were assigned to the placebo group. The groups were comparable at screening with respect to demographic variables. All randomized patients had medically refractory partial seizures and were young at diagnosis (mean age at diagnosis = 2.9 ±2.6 years). Mean baseline partial seizure frequency per 28 days was similar between gabapentin and placebo treatment groups (74.5±268.3; 63.3 ±103.8, respectively). A slightly higher proportion of gabapentin-treated patients completed the study (82.4% versus 78.1%).

- Efficacy results
  - Of the 247 randomized patients (ITT population), 8 placebo-treated and 6 gabapentin-treated patients were excluded from the MITT population because they had less than 28 days of baseline and/or double-blind seizure diary, or took less than 28 days of study medication. For the MITT population, the primary efficacy variable, RRatio for all partial seizures, was significantly lower (better) for gabapentin treated patients than for placebo-treated patients (ANOVA, least squares mean = -0.161 and -0.072, respectively; p = 0.0407). The supplemental analysis (ITT) did not show a significant difference in RRatio between the treatment groups (p = 0.1246). As there was evidence of non-normality in the distribution of the data, additional analyses were performed using rank-transformed data. These analyses demonstrated a significant difference in RRatio between treatment groups for both the MITT (p = 0.0103) and ITT (p = 0.0299) populations. CMH analysis of the complementary variable, responder rate, showed no significant difference between treatment groups for both the MITT and ITT populations. The median percent change for all partial seizures was -17.0% for gabapentin as opposed to -6.5% for placebo. Values for median PCH showed gabapentin to be most effective in controlling complex partial seizures (-35%) and secondarily generalized seizures (-28%), but less effective for simple partial seizures (-15%). The corresponding values for placebo were -12.0% (CP), +13.2% (SGTC), and -14.0% (SP). The global assessment of reduction in seizure frequency by parents/guardians was also significantly better for gabapentin (p = 0.046).

- Safety results

- More patients in the gabapentin group (63%) than in the placebo group (52%) had adverse events; however, for most patients in both treatment groups, these events were not considered related to treatment. The majority of patients who reported adverse events had a maximum intensity of mild or moderate. The types of adverse events that occurred were consistent with those in previous studies of add-on gabapentin therapy in adults, except for reports of concurrent childhood illnesses and emotional behavior changes. For both treatment groups, the respiratory system, body as a whole, the digestive system, and the nervous system were the most frequently affected body systems. Among gabapentin-treated patients, the most frequently reported adverse events (7 patients) were viral infection, fever, pharyngitis, nausea and/or vomiting, somnolence, hostility, and upper respiratory infection. There was a slightly higher incidence of emotional behavior changes (aggression, hyperactivity, emotional lability) with gabapentin than placebo, but the incidence of interventions for these types of events was similar between the 2 groups. The onset of adverse events for the gabapentin group occurred earlier than for the placebo group, but duration of adverse events was similar between the groups. No patients died during this study. Serious adverse events were infrequent in both treatment groups; only 2 events in the gabapentin treatment group (overdose of study drug and stupor due to overdose of study medication plus 3 other AEDs) were considered related to treatment. Three placebo-treated patients (2%) and 6 gabapentin-treated patients (5%) withdrew from the study because of 1 or more adverse events.

Conclusions Gabapentin as add-on therapy for partial seizures in children presents an efficacy profile similar to that previously found in adults: a significant reduction in seizure frequency in all partial seizures, with the greatest efficacy in secondarily generalized seizures. Gabapentin as add-on therapy is safe and well-tolerated in this paediatric population.

Assessor's comment:
The analysis results of this study indicates that in paediatric patients with epilepsy, gabapentin as add-on therapy is effective in controlling partial seizures, especial in secondarily generalized seizures. However, in our opinion the analysis of the data in a separate way for children younger than 5 years old and older than 6 years was important.
The profile of adverse events is according with the information of the SPC.

Study 945-87/187
Title: Open-Label Extension of a Double-Blind, Placebo-Controlled, Multicenter Study of Gabapentin (CI-945, Neurontin) as Add-On Therapy in Children With Partial Seizures

- **Description**
  - Study 945-87/187 was an open-label extension of a double-blind, placebo-controlled, parallel-group, multicenter study of gabapentin as add-on therapy in children with partial seizures (protocol 945-86/186). The study was conducted at 23 centers in the UK (945-87) and 30 centers in Europe, South Africa. and the US (945-187). Studied Period (years): 29/01/94 to 14/05/97

- **Methods**
  - Objective(s)
    - To evaluate the safety and long-term efficacy of gabapentin as add-on therapy in the treatment of paediatric patients with medically uncontrolled partial seizures.

  - Study design
    - Patients who participated in 2 previous double-blind studies (945-86, 945-186) and wanted to receive open-label gabapentin entered these studies. Patients could also enroll directly from baseline in 945-87. Patients receiving gabapentin during double-blind were maintained on their current dose. Patients who received placebo during double-blind or who enrolled directly from baseline initiated gabapentin treatment at 24 to 35 mg/kg/day. Patients in Study 945-187 could increase their dose to 60 mg/kg/day. Current AED therapy was maintained, adjusted, or discontinued, at the discretion of the investigator. The design and objectives of both double-blind studies were essentially the same, with the protocol-specified intention of allowing data to be pooled; similarly, the design and objectives of both open-label extension studies were essentially the same in order to allow data to be pooled as the protocol required.

  - Study population /Sample size
    - A total of 237 patients entered the open-label phase.
    - Paediatric patients with refractory partial seizures, who met the inclusion criteria for study 945-86/945-186, received at least 3 days of double-blind medication (Study 945 -187 only) and wished to receive gabapentin for an extended period.

  - Treatments
    - Open-label medication: Gabapentin 100 mg capsules, 300 mg capsules, 400 mg capsules
    - Administration: Oral capsules TID
    - Duration of Treatment: 24 weeks, plus a taper phase.

  - Outcomes/endpoints
    - Safety was evaluated using adverse events, serious adverse events, deaths, and withdrawals due to adverse events, results of clinical laboratory tests, and physical and neurological examinations.
    - Efficacy was not evaluated in this report.

  - Statistical Methods
    - No inferential statistical tests were conducted

- **Results**
  - Recruitment/ Number analysed
    - Of the 237 patients from 43 sites enrolled in the open-label study, 232 patients had received study medication in the double-blind study and 5 patients entered directly from baseline. Total exposure to gabapentin in the open-label study was 36,433 patient-days (100 patient-years). Most exposure to gabapentin, in terms of percent

of patients exposed and total dose days, occurred at doses between □20 and <40 mg/kg/day. The majority (71%) of the patients completed the open-label study.
- The most common reason for withdrawal was lack of efficacy (20% of the patients), followed by adverse event (6%).

- Safety results

  - Sixty-six percent of the patients experienced 1 or more adverse events during the open-label study; approximately half of these patients had an event considered associated with gabapentin treatment. Most adverse events were mild to moderate in intensity. The most frequent adverse events (>5% of patients) were pharyngitis, somnolence, rhinitis, nausea and/or vomiting, fever, upper respiratory infection, headache, viral infection, diarrhoea, convulsions, and emotional lability. Somnolence (8%), convulsions (4%), fatigue (3%), emotional lability (3%), hostility (3%), ataxia (3%), hyperkinesia (2%), and nervousness (2%) were the most frequent adverse events associated with gabapentin treatment.
  - There were no deaths in this study and the rate of withdrawal because of adverse events was low; serious adverse events were also infrequent.
  - There were no clinically important changes in laboratory parameters, neurological or physical examinations, or vital signs.

Conclusions Gabapentin is safe and well-tolerated in children with partial seizures between 3 and 12 years of age during extended treatment at doses up to and including 60 mg/kg/day.

Assessor's comment:
The profile of adverse events is according with the information of the SPC.

Study 945-305 and 945-405
Title: Gabapentin Paediatric Add-On Trial: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study in Paediatric Patients Aged 1 Month to 36 Months With Refractory Partial Seizures

- **Description**
  - Study 945-305/406 was an double-blind, placebo-controlled, parallel-group, multicenter study. The study, was conducted at 73 centers in the United States and Canada (945-305) and 15 international centers (945-405), was intended to evaluate the effect of gabapentin treatment on the frequency of partial seizures, evaluate the short-term safety of gabapentin treatment, and assess the pharmacokinetics of gabapentin treatment (using a population approach) in paediatric patients, 1 to 36 months of age, with epilepsy. Studied Period (years): 11/04/99 – 19/08/99

- **Methods**
  - Objective(s)
    - The objectives of this study were to evaluate the effect of gabapentin treatment on the frequency of partial seizures, evaluate the short-term safety of gabapentin treatment, and assess the pharmacokinetics of gabapentin treatment (using a population approach) in paediatric patients, 1 to 36 months of age, with epilepsy.

- Study design
  - This multicenter study used a randomized, double-blind, placebo-controlled, parallel-group design. Patients were initially entered in a screening period of variable length up to 2 weeks to confirm the diagnosis of partial seizures by clinical observation (plus additional criteria) or electroencephalogram (EEG) monitoring. Following screening, eligible patients entered a 3-day baseline phase, which included a target of 48 hours of video-EEG monitoring. During this 3-day baseline phase, patients maintained their concurrent antiepileptic drug (AED) therapy and additional AEDs were not added. At the end of the baseline phase, patients were randomly assigned to receive gabapentin (40 mg/kg/day given TID) or placebo treatment during a 3-day double-blind phase. During the double-blind phase, concurrent AED therapies remained unchanged and included a target of 72 hours of video-EEG monitoring. At the end of the double-blind phase, patients had the option either to discontinue study medication (study medication was tapered over a 2-day withdrawal period) or to enter an open-label gabapentin follow-on study (Protocol 945-301 or 945-401).

- Study population /Sample size
  - A total of 76 paediatric patients were randomly assigned to receive either gabapentin (40 mg/kg/day) or placebo treatment (38 patients per group).
  - Paediatric patients were males or females, 1 month to 36 months of age, weighing 3.5 to 20.0 kg, with partial seizures not adequately controlled by at least 1 current AED. Patients had at least one partial seizure during the screening period (within 2 weeks prior to baseline) either clinically observed or captured on EEG. If previously on gabapentin therapy, the patient must have ceased taking gabapentin at least 1 week prior to the start of the screening period. At screening, a 12-lead electrocardiogram (ECG) had no significant abnormality and a computed tomography (CT) scan (with contrast) or magnetic resonance imaging (MRI) of the head (previously or at screening) demonstrated no progressive structural abnormality. Each patient's parent or legal guardian was able to understand and comply with study instructions and procedures, and provided written informed consent.

- Treatments
  - Gabapentin syrup 50 mg/ml, TID
  - 3-day double-blind treatment phase, 2-day withdrawal period or entry into open-label treatment

- Outcomes/endpoints
  - The primary criterion to establish the efficacy of gabapentin was the response ratio (RRatio or symmetrised proportional change) for all partial seizures. The formula for the 28-day partial seizure rate was:

$$28\text{-day partial seizure rate} = \frac{\#\text{ of all partial seizures in phase}}{[\text{total recordable hours in phase}]} \times 24 \times 28$$

The response ratio compared the 28-day all partial seizure rates between baseline (B) and double-blind treatment (T) phases, and was calculated as:

T- B
T+ B
Where: T = 28-day all partial seizure rate during double-blind phase.
B = 28-day all partial seizure rate during baseline.
Secondary efficacy parameters were the responder rate (ie, the proportion of patients with at least a 50% reduction in all partial seizures between baseline and double-blind phases), the percent change in 28-day all partial seizure rate between the double-blind and baseline phases, and the proportion of patients who exhibited a decrease in secondarily generalized tonic-clonic (SGTC) seizures from the baseline phase to the double-blind treatment phase. Safety parameters included adverse events (nature, frequency, and severity), results of physical and neurological examinations, vital signs, body weight, 12-lead ECG, and clinical laboratory test results.

- Statistical Methods
  - The primary analysis of the RRatio was performed on the Intent-to-Treat (ITT) population, which was defined as all patients who were randomized to either of the 2 study treatments. The statistical comparison of the ranked RRratio between the 2 treatment groups was based on analysis of covariance using the rank transformation approach adjusting for the patient's gender ($\alpha \leq 0.05$, 2-sided). Descriptive statistics of the RRatio were provided for the 2 treatment groups and for the subgroups of male and female paediatric patients. The mean treatment difference and 95% CI for the difference between the 2 treatment groups were also calculated. In a supplementary analysis, the primary efficacy analysis was repeated for the observed cases, steady state, and evaluable populations.
  - Secondary Analyses were performed on the ITT population. The responder rate for each treatment group was analyzed using Fisher's exact test. Descriptive statistics for the percent change in 28-day partial seizure rates were presented, along with the number and percent of patients with percent change in 28-day partial seizure rates for quartiles of decrease or increase in percent change. The proportion of patients who exhibited a decrease in SGTC seizures was compared between the 2 treatment groups using Fisher's exact test. Since the primary analysis results from the ITT population did not differ from the results for the observed cases, steady state, or evaluable populations, the secondary analyses were conducted only in the ITT population.

➢ Results

- Recruitment/ Number analysed
  - A total of 76 paediatric patients, ranging in age from 1.9 months to 36 months, were randomly assigned to study treatment; 38 patients to placebo and 38 patients to gabapentin.

- Baseline data
  - More male (60.5%) than female (39.5%) paediatric patients enrolled in the study. Most patients in each treatment group were white, non-Hispanic (57.9% gabapentin-treated patients, 60.5% placebo-treated patients). The mean age of epilepsy onset was similar in each treatment group; 5.8 months of age for placebo-treated patients and 4.1 months of age for gabapentin-treated patients. All patients

were diagnosed with partial seizures and had a history either of simple partial seizures (71.1% placebo-treated patients, 78.9% gabapentin-treated patients) or SGTC seizures (63.2% placebo-treated patients, 65.8% gabapentin-treated patients) or both. All randomized patients received at least 1 dose of study medication. Thirty-six (94.7%) placebo-treated patients and 38 (100%) gabapentin-treated patients completed the double-blind treatment phase. Two placebo-treated patients withdrew early from the double-blind treatment phase and entered the open-label study: 1 patient withdrew due to lack of efficacy and 1 patient withdrew due to other administrative reasons.

- Efficacy results
  - Primary Efficacy Analysis: In the ITT population, gabapentin-treated patients had a mean RRatio of -0.048 and placebo-treated patients had a mean RRatio of 0.018. The difference in the RRatio between the treatment groups (gabapentin minus placebo), adjusted for gender, was -0.066. This difference was not statistically significant ($p = 0.369$). Similar results were seen for males and females separately. Although the gender-adjusted RRatio declined more for gabapentin-treated patients than for placebo-treated patients for all 4 populations (ITT, observed cases, steady state, and evaluable), none of these differences were statistically significant.
  - Secondary Analysis: The responder rate for all partial seizures was 13.2% for each treatment group ($p > 0.999$). The mean percent change in 28-day all partial seizure rates was -0.7% for gabapentin-treated patients and 14.0% for placebo-treated patients. Three patients in each treatment group had SGTC seizures. Two of the 3 placebo-treated patients exhibited a decrease in SGTC seizures, but none of the gabapentin-treated patients. No statistically significant difference between the 2 treatment groups was detected.

- Safety results
  - In the ITT population, treatment-emergent signs and symptoms (TESS) adverse events were reported for 22 (57.9%) gabapentin-treated patients and 14 (36.8%) placebo-treated patients. Most adverse events were mild or moderate. Skin and appendages was the most frequently affected body system for the placebo group and the digestive and nervous systems were the most frequently affected body systems for the gabapentin group. Frequently reported adverse events (reported for ≥5.0% of gabapentin-treated patients) were somnolence (15.8% gabapentin, 2.6% placebo), nausea and/or vomiting (13.2% gabapentin, 2.6% placebo), rash (5.3% gabapentin, 7.9% placebo), skin disorder (5.3% gabapentin, 5.3% placebo), constipation (5.3% gabapentin, 0% placebo), and otitis media (5.3% gabapentin, 0% placebo). The incidence of adverse events considered associated with study medication was lower in the placebo group (10.5%) than in the gabapentin group (23.7%). In the placebo group, the most frequently reported (2 patients) associated adverse event was rash, and in the gabapentin group, the most frequently reported associated adverse events were somnolence (6 patients) and nausea and/or vomiting (2 patients). One adverse event in a gabapentin-treated patient was severe (an increased level of an AED) and one was serious (upper respiratory infection) but unrelated to gabapentin treatment. No patient withdrew early due to

an adverse event and no patient died. Other safety evaluations were generally normal or similar to those seen in older children and revealed no safety issues of clinical concern.

- **Conclusions:** Gabapentin as adjunctive therapy in the treatment of refractory partial seizures in paediatric patients between 1 and 36 months of age is favourable, but did not reach statistical significance. Gabapentin was safe and well tolerated in this short study.

Assessor's comment:
The present study did not show efficacy of gabapentin as adjunctive therapy in the treatment of refractory partial seizures in paediatric patients between 1 and 36 months of age.
The profile of adverse event, in short –term use in paediatric patients between 1 and 36 month was similar to the older children.

Study 945- 301 and 945-401
Title: Open-Label, Safety Study of Gabapentin (CI-945) as Adjunct Therapy in Children Aged 1 Month Through 4 Years With Seizures Uncontrolled by Current Anticonvulsant Drugs

- **Description**
  - Study 945-301 945-401 was an open-label extension of an double-blind, placebo-controlled, parallel-group, multicenter study, was intended to evaluate the safety of gabapentin as add-on therapy in the treatment of paediatric patients 1 month through 4 years of age with seizures classified as partial, with or without secondary generalization, or as atonic, behavioral, clonic, tonic, or versive. The study was conducted at 51 centers in the United States and Canada (945-301) and 11 international centers (945-401). Studied Period (years): 16/04/99 – 16/07/01.

- **Methods**

  - Objective(s)
    - to determine the safety of gabapentin as add-on therapy in the treatment of paediatric patients 1 month through 4 years of age with seizures classified as partial, with or without secondary generalization, or as atonic, behavioral, clonic, tonic, or versive.

  - Study design
    - These open-label, multicenter studies accepted patients with epilepsy who wished to continue gabapentin therapy following their participation in double-blind, placebo-controlled, parallel-group studies of gabapentin (Protocols 945-305 and 945-405) or patients who met *de novo* entry criteria. The studies consisted of an open-label treatment phase of up to 104 weeks and a 6-day withdrawal phase. Beginning at Visit V2 of the open-label phase, gabapentin dosage levels could be increased to 60 mg/kg/day, and dosages of pre-existing and additional antiepileptic drugs (AEDs) could be changed at the discretion of the investigator.

  - Study population /Sample size
    - A total of 198 patients received at least 1 dose of open-label gabapentin.

- Treatments
  - Gabapentin (CI-945) was administered orally TID as a flavoured syrup (50 mg/mL). Batch numbers were CZ 1191097 and 903NOL.
  - **Duration of Treatment:** Up to 104-week open-label treatment phase, 6-day withdrawal phase.

- Outcomes/endpoints
  - Safety was assessed by adverse events (nature, frequency, and severity), clinical laboratory tests (hematology, blood chemistry, and urinalysis), physical and neurological examinations, and ECG. Safety was also assessed in conjunction with serum gabapentin and other AED concentrations.

- Statistical Methods
  - Not applicable; no efficacy assessments were performed.

Results

- Recruitment/ Number analysed
  - A total of 198 paediatric patients (96 males and 102 females) were enrolled. A total of 123 patients entered the study *de novo*, and 75 entered from 945-305 and 945-405. Most patients were white, non-Hispanic (66%), and the median age was 22.9 months (1.9-59.6 months).
  - .All 198 patients received at least 1 dose of gabapentin. Most patients were on doses of 40-60 mg/kg/day. Total exposure to gabapentin was 254 patient-years. The maximum number of days that any patient received gabapentin was 773 days. A total of 98 (50%) patients terminated early from the study. The primary reason for early termination was lack of efficacy.

- Safety results
  - Overall, 188 patients (95%) had an adverse event. Of these patients, 88 (44%)had a TESS adverse event (TESS = treatment-emergent signs and symptoms) considered associated with gabapentin. The maximum intensity of adverse events was mild for 53 patients, moderate for 84 patients, and severe for 51 patients. The respiratory system (77%), the body area whole (65%), and the digestive system (56%) were the most frequently affected body systems. The most frequently reported adverse events (reported by at least 20% of patients) were fever, upper respiratory infection, somnolence, pneumonia, rhinitis, otitis media, pharyngitis, and nausea and/or vomiting. The most common associated adverse events were somnolence (22%), nervousness (6%), and ataxia (5%). Overall, the median time to onset for adverse events was 10 days, and the overall median duration of adverse events was 9 days. Serious adverse events were reported for 75 patients (38%). One of the serious adverse events (hematuria) was considered possibly associated with gabapentin treatment. Sixteen patients (8%) withdrew early from the study due to adverse events. Seven of the events leading to withdrawal were considered possibly or probably related to study medication. Eight deaths occurred during the study due to the following adverse events: sepsis (2 patients), coma,

pneumonia (2 patients), cardiorespiratory failure, respiratory distress, and respiratory disorder.
- Among the very low and very high laboratory values reported, leukocytosis, neutropenia, thrombocytosis, thrombocytopenia, elevated amylase, and elevated alkaline phosphatase were the most common.

Conclusions: Treatment with gabapentin as add-on antiepileptic therapy was well tolerated in this paediatric patient population. Although almost half of the patients experienced a treatment-associated adverse event, most adverse events were typical of early childhood illnesses and their complications.

Assessor's comment:
The profile of adverse events is according with the information of the SPC.

Monotherapy studies

Study 945-094
Title: Gabapentin Paediatric Monotherapy Trial: A Multicenter, Double-Blind, Placebo-Controlled, Parallel-Group Study in Paediatric Patients With Benign Childhood Epilepsy With Centrotemporal Spikes (BECTS)

- **Description**
  - Study 945-094 was a double-blind, placebo-controlled, parallel-group, multicenter study. The study, was conducted at 70 centers in the United States and Canada, was intended to evaluate, in paediatric patients with BECTS, the safety and efficacy of gabapentin administered as monotherapy by comparing gabapentin treatment with placebo treatment, and to assess the behavioral/cognitive effects of gabapentin in that patient population. Studied Period (years): 17/08/1994 to 13/01/98

- **Methods**
  - Objective(s)
    - To evaluate, in paediatric patients with BECTS, the safety and efficacy of gabapentin administered as monotherapy by comparing gabapentin treatment with placebo treatment, and to assess the behavioral/cognitive effects of gabapentin in that patient population.

  - Study design
    - Patients were randomly assigned to receive gabapentin (30 mg/kg/day) or placebo. Patients were maintained on study treatment for 36 weeks or until they experienced an exit event (1 secondarily-generalized tonic-clonic seizure; 3 partial seizures; status epilepticus; or seizure activity that was increased in intensity or severity or was unacceptable to the patient/parent/guardian or investigator).

  - Study population /Sample size

- A total of 226 patients were randomly assigned to treatment: 114 to gabapentin and 112 to placebo.
- Patients were 4 to 13 years of age and had BECTS with partial or secondarily-generalized tonic-clonic (SGTC) seizures (minimum of 1 and maximum of 10 partial or SGTC seizures within the 6 months prior to study entry). Patients (a) had never been treated with antiepileptic drugs (AEDs), (b) were currently taking one marketed AED and wished to change medication, or (c) were previously treated in the past 2 years but were not currently taking a marketed AED.

- Treatments
  - Oral capsules of 100 mg or 200 mg
  - Dose 30 mg/Kg/dia TID
  - Duration: Gabapentin and placebo treatment groups: 36-week evaluation phase.

- Outcomes/endpoints
  - The primary efficacy parameter was time to exit. Secondary efficacy parameters were completion rate, mean time on treatment, and exit rate. Behavioral/cognitive function was assessed by evaluating patient performance in the areas of behavior, motor skills, cognition, and memory.
  - Safety was assessed on the basis of adverse event reports, results of clinical laboratory tests, physical and neurological examinations, and electrocardiogram (ECG) results.

- Statistical Methods
  - The distribution of time to exit was estimated using Kaplan-Meier survival analysis and was compared between treatment groups using the log-rank test; data for patients who had no exit event were censored. This primary efficacy analysis was performed on the intent-to-treat (ITT) and efficacy-evaluable (EE) populations. Time to exit was also compared between treatment groups for the ITT population using the log-rank test for each of 2 AED status categories at screening (0 AEDs and □1 AED). In an exploratory analysis, the effect of AED status at screening on time to exit was compared between treatment groups (ITT population) using Cox regression methods.
  - Completion rate was compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) chi-square test adjusted for center. A 95% confidence interval was calculated for the treatment difference comparison, gabapentin minus placebo. Generalizability was examined using the Breslow-Day test. These analyses were performed on the ITT and EE populations. Mean time on treatment was compared between treatment groups for the ITT and EE populations using a Kruskal-Wallis ranked analysis of variance (ANOVA) with treatment and center in the model. The exit rate was compared between treatment groups overall and by each type of exit event using a CMH chi-square analysis adjusted for center. This analysis was performed on the ITT population only. A 95% confidence interval was calculated for the treatment group difference in overall exit rate, gabapentin minus placebo.

- **Results**

- Recruitment/ Number analysed
  - A total of 226 patients ranging in age from 4 to 13 years entered the double-blind treatment phase. Of these, 114 patients (70 boys and 44 girls) with a mean age of 7.9 years were randomly assigned to the gabapentin treatment group and 112 patients (65 boys and 47 girls) with a mean age of 8.4 years were randomly assigned to the placebo group. The groups were comparable at screening with respect to demographic variables. All patients received at least one dose of study medication, except one patient assigned to gabapentin treatment. This patient did not take any study medication and was subsequently withdrawn from the study and excluded from the ITT and evaluable populations. A higher proportion of gabapentin-treated than placebo-treated patients completed the 36-week treatment period (47.8% versus 34.8%). The most frequently reported reason for early termination in both treatment groups was occurrence of a third partial seizure (29.2%, gabapentin; 30.4%, placebo). More gabapentin-treated patients withdrew due to adverse events (3.5% versus 0.0%), whereas more placebo-treated patients withdrew due to noncompliance (8.0% versus 1.8%).

- Baseline data
  - A total of 226 patients were randomly assigned to treatment: 114 to gabapentin and 112 to placebo. Of the 226 patients, there were more boys (60%) than girls (40%), which is consistent with the clinical profile of BECTS. The mean age was 7.9 years in the gabapentin treatment group and 8.4 years in the placebo group. The mean age of patients at the time of diagnosis of BECTS was similar between the 2 treatment groups. Few patients in either treatment group had a family history of BECTS, and the highest incidence rate of epilepsy among family members was reported for grandparents (5.3%, gabapentin; 11.6%, placebo). A history of simple partial, complex partial, and SGTC seizures was reported for approximately 50%, 40%, and 60% of the patients, respectively, in each treatment group. Although 48.2% and 57.1% of the patients in the gabapentin and placebo groups, respectively, had been treated with an AED at some time prior to the study, only 28.1% of patients in the gabapentin group and 38.4% in the placebo group were currently taking any AED at screening. Carbamazepine was the most commonly used AED in both treatment groups.

- Efficacy results
  - Of the 226 patients randomized to treatment, 8 gabapentin-treated and 5 placebo-treated patients were excluded from the evaluable population because of protocol violations. For the ITT population, the median time to exit was greater in gabapentin-treated patients (67 days) compared with placebo-treated patients (40.5 days). The primary efficacy analysis of time to exit demonstrated a trend towards a statistically significant difference between the treatment groups for the ITT population (log-rank test comparing Kaplan-Meier survival curves, $p = 0.085$). The difference for the evaluable population analysis was statistically significant ($p = 0.023$). Results of the secondary efficacy analyses (completion rate, mean time on treatment, and exit rate) favoured gabapentin (higher completion rate, longer time on treatment, and lower exit rate); however, the differences in results between the treatment groups did not reach statistical significance in either

analysis population (ITT or evaluable). All mean changes in behavioral/cognitive function test results, whether for gabapentin or placebo treatment, reflected improvement in performance.

- Safety results
  - More patients in the gabapentin group (81%) than in the placebo group (72%) experienced adverse events; however, for most patients in both treatment groups, these events were not considered by the investigator associated with study treatment. Most patients who reported adverse events had a maximum intensity of mild or moderate. The types of adverse events reported in this study were often attributable to common childhood illnesses. The respiratory system and body as a whole were the most frequently affected body systems for the gabapentin and placebo treatment groups, respectively. Among gabapentin-treated patients, the most frequently reported adverse events (6 or more patients in a treatment group) were headache, rhinitis, viral infection, upper respiratory infection, pharyngitis, coughing, abdominal pain, sinusitis, emotional lability, nausea and/or vomiting, rash, hyperkinesia, nervousness, dizziness, fever, diarrhea, and inner ear infection. There was a higher incidence of emotional behaviour changes (emotional lability, hyperkinesia, hostility, personality disorder, suicidal) in the gabapentin group (16.8%) than in the placebo group (5.4%), but intervention (discontinuation or dose interruption) for these types of events was infrequent in both groups. The overall median time to onset of adverse events and duration of adverse events was similar for the 2 treatment groups. No patients died during this study. Serious adverse events occurred in a slightly higher proportion of gabapentin-treated patients (5.3% versus 0.9%); none of the serious adverse events were considered by the investigator associated with study medication. Four patients, all in the gabapentin group, were withdrawn from the study because of one or more adverse events. All the adverse events leading to withdrawal affected psychobiologic function (emotional lability or abnormal thinking) or the nervous system (hyperkinesia); these events were moderate in intensity and considered by the investigator as associated (possibly or probably) with study drug.

Conclusions: Gabapentin, in comparison to placebo, tended to demonstrate better seizure control in children with BECTS using time to exit, completion rates, exit rates, and time on treatment as measures of seizure control. This treatment effect was statistically significant in the evaluable patient population, and trended towards statistical significance in the ITT patient population. Gabapentin was safe and well-tolerated in this patient population.

Assessor's comment:
The safety profile of gabapentin in this study is according with the information of SPC of this product.

Study 945- 095
Title: An Extended Open-Label Gabapentin (CI-945) Paediatric Monotherapy Trial Following A Double-Blind Study (Protocol 945-094) in Paediatric Patients With Benign Childhood Epilepsy With Centrotemporal Spikes (BECTS)

- **Description**
  - Study 945-095 was an open-label extension of a double-blind, placebo-controlled monotherapy study of gabapentin (Protocol 945-094) in patients with BECTS . The study was conducted at 70 centers in the United States and Canada Studied Period (years): 13/09/94 through 22/12/98.

- **Methods**

  - Objective(s)
    - To evaluate the long-term safety of gabapentin monotherapy in paediatric patients with BECTS.

  - Study design
    - This study was designed to accept patients with BECTS who wished to continue gabapentin monotherapy following their participation in a double-blind, placebo-controlled monotherapy study of gabapentin (Protocol 945-094). The study consisted of a 3-day, blinded transition period and a 96-week, open-label treatment period. During the transition period, gabapentin dosages were adjusted to a common dose of 30/mg/kg (by Day 3). During the open-label phase, gabapentin dosages could range from 15 to 60 mg/kg/day.

  - Study population /Sample size
    - A total of 191 patients were enrolled.

  - Treatments
    - Gabapentin 100 mg, 200 mg, 300 mg and 400 mg. Oral capsules TID
    - Duration of Treatment: 3-day transition phase and 96-week treatment phase

  - Outcomes/endpoints
    - Criteria for Evaluation: Behavioral/cognitive function was assessed by evaluating patient performance in the areas of behavior, motor skills, cognition, and memory. Safety was assessed on the basis of adverse event reports, physical and neurological examinations, and ECG results. Results of clinical laboratory tests (hematology, blood chemistry, and urinalysis) were collected and evaluated through July 31, 1997.

  - Statistical Methods
    - No descriptive summarization or inferential testing of efficacy data was performed.

- **Results**

  - Recruitment/ Number analysed
    - A total of 191 patients ranging in age from 4 to 14 years entered the open-label treatment phase. Most patients were white (75.9%) and the mean age was 8.7 years. Overall, 54 (28.3%) patients completed the 96-week open-label treatment period. The most frequently reported reasons for early termination were

other/administrative (63 [33.0%] patients), followed by lack of compliance (20 [10.5%] patients), and lack of efficacy (19 [9.9%] patients).

- Behavioral/Cognitive Function: Mean changes in behavioral/cognitive function test scores reflected stable patient performance since testing performed during the 945-094 study.

- Safety results

  - Overall, 162 (84.8%) patients had an AE. Sixty-six (34.6%) patients had TESS adverse events considered to be associated with treatment. Most adverse events had a maximum intensity of mild or moderate. The respiratory system and body as a whole were the most frequently affected body systems. Frequently reported AEs, (reported by more than 7.0% of patients) included headache, pharyngitis, upper respiratory infection, viral infection, rhinitis, abdominal pain, fever, coughing, sinusitis, emotional lability, otitis media, dizziness, and nausea and/or vomiting. Adverse event reports of emotional behavior change were similar in frequency and severity to those seen in the controlled trial (Study 945-094). Overall, the median time to onset for adverse events was 20 days and the median duration of adverse events was 10 days. Serious adverse events were reported for 10 patients. None of the serious adverse events were considered associated with gabapentin treatment. Six patients withdrew early from the study due to AEs. All of the adverse events leading to withdrawal were mild or moderate in intensity. No deaths occurred during the study. No significant trends in mean changes from screening to final visit were observed for vital signs, and minimal changes were observed in clinical laboratory results or from ECG evaluations.

Conclusions: Long-term treatment with gabapentin was safe and well-tolerated in this patient population.

Assessor's comment:
The profile of adverse events is according with the information of the SPC.

Others studies in paediatric populations

Study 877-034
Title: Open-label extension of an open-label, pilot study of safety and tolerance of gabapentin capsules as add-on therapy in the treatment of juvenile patients with partial seizures

- **Description**
  - Open label study, in 1 center, period os the study 08/01/86 – 27/04/89
- **Methods**

  - Objective(s)

OBJECTIVE The objective of this study was to evaluate safety and tolerance with open-label treatment of gabapentin as add-on therapy in juvenile patients with medically refractory partial seizures.

- Study design
  - Open-label study of gabapentin treatment

- Study population /Sample size
  - Total of 4 patients with a range of 5 through 14 years (2 males, 2 females) were pre-medicated whit one(1), two(2), or four (1) antiepileptic drugs.
  - Two patients withdrew due to lack of efficacy and two patients due to other reasons

- Treatments

DRUG TREATMENT[3] Dosages of gabapentin were administered TID and were adjusted to provide optimal seizure control without unacceptable side effects, with a maximum allowable dosage of 900 mg/day gabapentin. Patients were treated for 36, 85, 88, or 1206 days with gabapentin at dosages up to 600 mg/day (4.4-14.7 mg/kg/day) and were generally compliant.

- **Results**
  - Efficacy results

EFFICACY[5] Subjective global evaluations of seizures and general condition of the patient were evaluated as a measure of efficacy. The ratings performed by physician and patient's parent were generally in agreement. Parental and physician's posttreatment evaluation of patient's seizures as compared to baseline in Study 877-034 indicated one patient had marked improvement and three patients had no improvement. Parental posttreatment evaluation of patient's general condition indicated three patients had improvement and one patient had none.

- Safety results

SAFETY[6-14] During the study, no patient had an adverse event[6], although one patient (Patient 2) was hospitalized three times to effect seizure control[7]. Results from clinical examinations[8], neurological examinations[9], EEGs[10], vital signs[11], gabapentin plasma levels[12], and plasma levels of concurrent antiepileptic drugs[13] were generally unchanged throughout the study. The following potentially clinically important deviations in clinical laboratory values[14] for two patients were considered to have possible clinical importance. Patient 1 had potentially clinically important increases in WBC without reported concomitant clinical findings during the study. Deviations were transient and returned to baseline values. The SGOT values were elevated slightly throughout the study and qualified as a potentially clinically important increase at the end of the study. Patient 6 had elevated values for hemoglobin and hematocrit at baseline and subsequent testing on Days 147, 189, and 231 indicated potentially clinically important decreases for these parameters, although the values were within normal limits.

Assessor's comment:
The number of patients of this study is too small; no new safety alert was raised by this study.

Study 945-19/20 and **Study** 945-49/50
Title: 2 double-blind, placebo-controlled, multicenter studies and their associated extended-treatment studies of the safety and efficacy of gabapentin monotherapy in patients with childhood absence epilepsy naïve to antiepileptic drug therapy (double-bind protocols 945-19 [US] and 945-20 [NON-US] and extended-treatment protocols 945-49 [US] and 945-50 [NON-US])

- **Description**
  - Study 945- 19/ 20 was an double-blind, placebo-controlled, parallel-group, multicenter study and Study 945-49/50 was an open-label extended-treatment extension of the previous study. This studies, was conducted at nine study centers in US and 8 study centers outside the US. The objective of the double-blind studies were to determine the efficacy and safety of gabapentin compared with placebo (PLC) when used as initial treatment in children with newly diagnosed childhood absence epilepsy. The objectives of the extended-treatment studies were to evaluate the long-term safety and efficacy of gabapentin in patients who had received therapeutic benefit from gabapentin treatment during the double-blind studies. Studied Period (years): 15/08/89 Through 12/07/91

- **Methods**
  - Objective(s)
    - The objectives of the double-blind studies were to determine the efficacy and safety of gabapentin 15 to 20 mg/kg/day compared with placebo (PLC) when used as initial treatment in children with newly diagnosed childhood absence epilepsy. The objectives of the extended-treatment studies were to evaluate the long-term safety and efficacy of gabapentin in patients who had received therapeutic benefit from gabapentin treatment during the double-blind studies.

  - Study design
    - Studies 945-19 (US) and 945-20 (non-US) were 8-week, multicenter studies comprising 2 weeks of double-blind, randomized, placebo-controlled treatment and 6 weeks of open-label gabapentin treatment. Patients receiving benefit could continue to receive gabapentin under extended-treatment Studies 945-49 (US) and 945-50 (non-US). In the double-blind phase, patients were randomly assigned to receive either gabapentin or PLC for 2 weeks. In the first 2 days of the double-blind phase, patients randomized to gabapentin treatment received one-third of the target daily dose (6-10 mg/kg/day) in the evening of Day 1 and two-thirds of the target daily dose (10-15 mg/kg/day) on Day 2 on a twice daily (BID) schedule. On Days 3 through 14, the fixed-dose treatment interval, the patients received the target daily dose (15-20 mg/kg/day) administered as equal divided doses 3 times a day (TID). Patients who completed the double-blind phase and elected to continue treatment in the open-label phase titrated in a blinded fashion onto open-label gabapentin (15-20 mg/kg/day). Beginning on Day 28 of the open-label phase, dosage adjustments between 8 and 35 mg/kg/day were allowed. This dosage range (8-35 mg/kg/day) was also used in the extended treatment studies.

  - Study population /Sample size

- A total of 33 patients were randomized; 18 received PLC and 15 received gabapentin. All 33 patients entered the open-label phase, and 13 patients subsequently entered the extended open-label phase.
- Medically naive patients 4 through 16 years of age, weighing between 18 and 70 kg (40-154 lb), with childhood absence epilepsy that had been confirmed and quantified by a screening electroencephalogram (EEG) were eligible for entry into the study.

- Treatments
  - Gabapentin capsules 100 or 200 mg
  - **Duration of Treatment:** 8 weeks, plus possible extended treatment

- Outcomes/endpoints
  - The primary efficacy criterion was change in seizure frequency from baseline to treatment (end of double-blind 24-hour EEG record). Two primary efficacy variables were used for this evaluation: Response Ratio (RRatio) and Responder Rate.

- Statistical Methods
  - Primary efficacy analyses were conducted on data from the double-blind phase. The RRatio was analyzed by Analysis of Variance (ANOVA). The Responder Rate was analyzed using Fisher's Exact test (2-sided).

- **Results**

- Recruitment/ Number analysed
  - Thirty-three patients participated in the 2-week double-blind phase of Studies 945-19 and 945-20. The population from both studies combined comprised 18 patients, 9 males and 9 females, with a mean age of 8.4 years who were randomly assigned to the placebo group; and 15 patients, 6 males and 9 females, with a mean age of 8.3 years who were assigned to the gabapentin group. Patient characteristics at screening showed no statistically significant differences between treatment groups.
  - Thirty-three patients entered and 21 (64%) completed the open-label phase. Thirteen (62%) of the 21 patients who completed the open-label phase entered the extended-treatment studies.
  - Table 1 gives characteristics and disposition of the patients in these studies.

TABLE 1. Patient Characteristics and Disposition

	Studies 945-19 and 945-20			Studies 945-49 and 945-50
	Double-Blind		Open-Label	Extended-Treatment
	PLC	GBP		
Randomized (Enrolled)	18	15	(33)	(13)
Characteristic				
Sex, N (%)				
Males	9 (50)	6 (40)	15 (46)	6 (46)
Females	9 (50)	9 (60)	18 (55)	7 (54)
Age, yrs				
Mean	8.4	8.3	8.4	8.1
Range	5-12	4-12	4-12	4-12
Weight, kg				
Mean	35.1	34.3	34.7	34.4
Range	21-64	19-51	19-64	19-57
Disposition				
Withdrawn				
Adverse Event	0	0	1	0
Noncompliance	0	0	1	0
Lack of Efficacy	0	0	10	10
Personal Reason	0	0	0	1
Administrative Reason	0	0	0	1
Completed Phase	18	15	21	1[a]

GBP = Gabapentin.
[a] One patient was receiving GBP when these studies were discontinued.

- Baseline data

TABLE 6. Patient Characteristics: Randomized Patient Population at Entry Into Studies 945-19 and 945-20

	Placebo N = 18	Gabapentin N = 15	Total N = 33
Sex, N (%)			
Males	9 (50.0)	6 (40.0)	15 (45.5)[a]
Females	9 (50.0)	9 (60.0)	18 (55.5)
Race, N (%)			
White	16 (88.9)	13 (86.7)[a]	29 (87.9)
Black	0 (0.0)	1 (6.7)	1 (3.0)
Other	2 (11.1)	1 (6.7)	3 (9.1)
Weight, kg			
Mean	35.1	34.3	34.7
Range	21-64	19-51	19-64
Age, yrs			
Mean	8.4	8.3	8.4
Median	8.5	8.0	8.0
Range	5-12	4-12	4-12
Duration of Epilepsy, yrs			
Median	<1	<1	<1
Range	<1-4	<1-2	<1-4
Etiology, N (%)			
Unknown	12 (66.7)	12 (80.0)	24 (72.7)
Family History of Epilepsy	6 (33.3)	3 (20.0)	9 (27.3)

[a] Percentage does not sum to 100% due to rounding.

- Efficacy results

  - Primary analyses were carried out on data from the double-blind phase for 31 of 33 children in the intent-to-treat population and 28 of 33 patients in the evaluable population. The intent-to-treat analyses showed Adjusted Mean RRatios for the intent-to-treat population were -0.110 for the placebo group and 0.059 for the gabapentin group, which were not significantly different. Similarly, no significant treatment differences were observed for Responder Rate. Results for the evaluable population were essentially the same with no significant treatment differences observed. During the open-label phase and extended-treatment studies, results on

these same response measures (RRatio and Responder Rate) were not considered clinically important.

- Safety results
  - During the double-blind phase, a total of 8 (44%) of 18 patients in the PLC group and 6 (40%) of 15 patients in the gabapentin group had adverse events. Somnolence and dizziness, the only adverse events experienced by more than 1 patient in each treatment group, were more frequent among gabapentin- than PLC-treated patients. During open-label, 22 of 33 patients (67%) reported 56 adverse events and during extended-treatment phases 7 of 13 (54%) reported 40 adverse events. The majority of adverse events during the double-blind and extended-treatment studies were mild or moderate in intensity. One PLC-treated patient was hospitalized during the double-blind phase for abdominal pain and nausea that began on Day -1. In the open-label phase, 3 patients on GBP were hospitalized with seizures, and 1 patient had a moderate rash considered serious and clinically important by the investigator that resolved with a dosage reduction. In the extended-treatment studies, no new or unexpected adverse events were seen during long-term treatment of 7 patients for at least 6 months, 2 patients for at least 1 year, and 1 patient for at least 1.5 years. No deaths occurred. There were no clinically important changes in clinical laboratory values, electrocardiograms, physical examinations, or neurological examinations.

Conclusions In children naive to antiepileptic therapy, gabapentin did not reduce or exacerbate absence seizure frequency compared with placebo. Gabapentin therapy was safe and well-tolerated during double-blind and open-label treatment at maximum oral dosages ranging from 9.6 to 47.8 mg/kg/day as evidenced by minimal side effects and only 1 withdrawal due to an adverse event. No new or unexpected adverse events were seen during long-term gabapentin treatment for up to1.5 years.

Study 945/08

Title: A Double-Blind, Placebo-Controlled, Multicenter Study, With an Open-Label Extension, of the Safety and Efficacy of Gabapentin as Add-On Therapy in the Treatment of Pharmacotherapy- Resistant Childhood Symptomatic Epilepsies

- **Description**
  - Study 945-08 was an 5 phases study with a double-blind, placebo-controlled, phase and an open-label phase. This studies, was conducted at 2 centers in Canada. The objective of this study was to evaluate the efficacy and safety of gabapentin when used as add-on therapy in highly therapy-resistant patients with symptomatic generalized epilepsy. Studied Period (years): 05/05/90 through 16/01/93

- **Methods**
  - Objective(s)
    - The objectives of this study were to evaluate the efficacy and safety of gabapentin when used as add-on therapy in highly therapy-resistant patients with symptomatic generalized epilepsy.

- Study design
  - The study was divided into 5 phases: an 8-week baseline, a 2-day titration, a 12-week double-blind, a 4-week interim continuation (during which, patients continued to receive the same blinded medication as during the double-blind), and a 12-week open-label phase. Following the 12-week open-label phase, patients had the option of continuing gabapentin treatment in an extended open-label phase of indeterminate length. In this report, the titration phase and the interim continuation phases were evaluated as part of the double-blind phase, and data from both the open-label and extended open-label phases were summarized together.

- Study population /Sample size
  - Total of 16 patients, initially 7 in the placebo group and 9 in gabapentin group.

- Treatments
  - Gabapentin capsules 100 and 200 mg

- **Results**

- Recruitment/ Number analysed
  - A total of 9 patients received gabapentin during the double-blind phase, 8 of whom completed 12 weeks of treatment. Seven of the patients randomized to gabapentin and 5 of the patients randomized to placebo continued or began gabapentin treatment in the open-label phase. Five of these patients also continued to receive gabapentin during an extended (ie, >12 weeks) open-label phase. Thus, a total of 14 patients, including 8 patients age 12 years or older, received gabapentin during the study.
  - Of the 16 patients that entered double-blind, 14 (88%) completed the phase. There were no differences in the number of withdrawals between the treatment groups. A total of 12 patients entered the open-label phase. Two of these patients completed a minimum of 12 weeks of open-label exposure but did not enter the extended open-label phase. Five patients withdrew due to a lack of efficacy either during the open-label or the extended open-label phase. Three other patients withdrew during the open-label phase for unknown reasons. The remaining 2 patients were in the extended open-label phase when they terminated from the study, again for unknown reasons.

- Efficacy results

  - Because the minimum number of patients needed for valid analysis of efficacy did not enroll in the study, only safety data were evaluated.

- Safety results
  - During the double-blind phase, 86% of placebo-treated patients and 100% of the gabapentin-treated patients experienced at least 1 adverse event. In the open-label phase, the 59% of patients had an adverse event. Three gabapentin-treated patients experienced severe adverse events (convulsions, ataxia or metabolic disorder)

during the double-blind phase, and 2 patients experienced severe adverse events (pneumonia) during the open label phase. Some of these events also met the criteria for serious adverse events. Two placebo-treated patients and 3 gabapentin-treated patients experienced serious adverse events during the double-blind phase; 2 of these patients (1 from each randomized group) also experienced serious adverse events during open-label. No patients were withdrawn from the study due to adverse events. One placebo-treated patient was withdrawn from the study on the recommendation of the Parke-Davis medical monitor, following the diagnosis of an electrocardiogram (ECG) abnormality present at baseline. Because this condition was present before the study drug was administered, it was considered a withdrawal for administrative reasons. There were no deaths during the study.

CONCLUSION: Gabapentin was well-tolerated in this study.

Study 945-188
Title: A study in healthy volunteers to determine the taste acceptability of 3 gabapentin (CI-945) liquid formulations

- **Description**
  - Study 945-188 was a single-blind, single-dose, randomized 3-way crossover taste test to evaluate the taste acceptability of 3 gabapentin liquid formulations. Studied Period (years): 05/11/94 to 11/11/94
- **Methods**
  - Objective(s)
    - To evaluate the taste acceptability of 3 gabapentin liquid formulations
  - Study design
    - The study was a single-blind, single-dose, randomized 3-way crossover taste test in healthy young subjects meeting entrance criteria. The trial was conducted under medical supervision.
  - Study population /Sample size
    - 93 subjects participated in the taste test
    - Good health, as determined by medical history, physical examination and clinical laboratory measurements; 12 to 15 years of age (inclusive); males and females (females to be sexually inactive or using a reliable method of birth control); and absence of significant urine concentration of any drug that could interfere with the taste test.
  - Treatments
    - 20-mg/mL gabapentin liquid formulation (Lot CF 0770794, Code 375); blueberry flavor 20-mg/mL gabapentin liquid formulation (Lot CF 0780794, Code 190); blueberry flavor 20-mg/mL gabapentin liquid formulation (Lot CF 0790794, Code 458); strawberry flavor
    - Administration: Oral, 5 mL (not to be swallowed)
  - Outcomes/endpoints

- Subjects tasted and then rated each formulation for bitterness, sweetness, and overall flavor on a scale of I to 5: 1 = Dislike extremely; 2 = Dislike moderately; 3 = Neither like nor dislike; 4 = Like moderately; 5 = Like extremely. Safety evaluation consisted of description of subjects' demographic characteristics, and the following procedures were performed at study screening and closeout: physical examination, collection of blood and urine samples for the evaluation of hematology, clinical chemistry, urinalysis, and pregnancy.

- Statistical Methods
  - The acceptability attributes were compared for each formulation with a crossover analysis of variance (ANOVA) model. The model consisted of sequence, subject-within sequence, period, and treatment terms. Ninety-five percent confidence intervals of the differences among formulations were reported.

- **Results**
  - Conclusions: The mean attribute ratings for each of the formulations evaluated fell within the mid to lower end of the rating scale. This indicates that overall the products were neither liked nor disliked, or were moderately disliked. However, of the 3 formulations evaluated, Code 458 (strawberry flavor) was ranked significantly higher and was perceived as more acceptable. Code 190 (blueberry flavor) was ranked the second highest, and Code 375 (blueberry flavor) was ranked the lowest.

Clinical overview

In the clinical overview presented by the MAH was made a analyses of published scientific literature, clinical studies in paediatric patients (some of which were significantly younger than the current minimum age of 6 years) over extended periods of up to 2 years, the Pfizer postmarketing safety database, and previously submitted PSURs. Adverse events were compared with those listed in SPC Section 4.8 Undesirable effects. Cases of Drug exposure during pregnancy were also evaluated and compared with the information available in SPC Section 4.6 Pregnancy and lactation.

Safety review

The Pfizer safety database was searched for medically confirmed adverse events over the period from the international birth date of 05 February 1993 through 31 August 2009. The database contains cases of adverse events reported spontaneously, cases reported by health authorities, cases published in the medical literature, and cases of serious adverse events reported from clinical studies and from Pfizer-sponsored marketing programs (solicited cases) regardless of causality. The safety database was searched for all gabapentin cases in children, which was defined as patient age having been reported as less than or equal to 17 years or the patient having been described as adolescent, child, infant, or neonate. It should be noted that gabapentin is indicated as monotherapy in the treatment of partial seizures with and without secondary generalization in adults and children over 12 years of The Pfizer safety database was searched for medically confirmed adverse events over the period from the international birth date of 05 February 1993 through 31 August 2009. The database contains cases of adverse events reported

spontaneously, cases reported by health authorities, cases published in the medical literature, and cases of serious adverse events reported from clinical studies and from Pfizer-sponsored marketing programs (solicited cases) regardless of causality. The safety database was searched for all gabapentin cases in children, which was defined as patient age having been reported as less than or equal to 17 years or the patient having been described as adolescent, child, infant, or neonate. It should be noted that gabapentin is indicated as monotherapy in the treatment of partial seizures with and without secondary generalization in adults and children over 12 years of age and as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and children aged 3 years and older in some locations, but in children aged 6 years and older in Europe. Gabapentin is not indicated for the treatment of neuropathic pain in patients younger than 18 years.
…

The search of the database identified 650 cases in children in the cumulative period (05 February 1993 through 31 August 2009). Mean patient age was 10.1 years (range, newborn to 17 years). The most frequently reported indications in this population were seizure-related (274), ill-defined disorder (120), and unknown (57). The majority of the cases originated from the United States (371); the majority of the remaining cases originated from United Kingdom (90), Japan (57), France (53), Canada (18), and Germany (17). The frequency of adverse events in the population 17 years or younger was compared with that for the same events in an adult population (adults and elderly). The following adverse events were reported in at least 2% of the paediatric population and at a frequency at least 3-fold that observed in the non-paediatric population: Abnormal behaviour, Aggression, Drug exposure during pregnancy, and Psychomotor hyperactivity. Drug exposure during pregnancy involved 64 cases in which paediatric patients were exposed to gabapentin and/or another antiepileptic medication *in utero*. The latency of gabapentin use to onset of events such as Psychomotor hyperactivity, Abnormal behavior, Aggression, and/or Agitation was generally unknown.

When the database was searched in the population of interest from 01 April 2008 (date since the most recent PSUR of 01 February 2005 through 31 March 2008) through
31 August 2009, 52 relevant cases were reported. The most frequently reported adverse events were Somnolence (7), Drug exposure during pregnancy (6), Agitation (5), Aggression (3), Hypotonia neonatal (3), and Insomnia (3). During this period, the following were reported in at least 3 cases in the paediatric population and at a frequency at least 3-fold higher than that observed in the non-paediatric population: Aggression, Agitation, Drug exposure during pregnancy, and Hypotonia neonatal.

Fourteen of 52 cases were reported in a literature abstract/medical meeting presentation in Japan. Most contain limited information and are missing pertinent data such as medical history, concomitant medications, and latency. The following events were reported in at least 2 cases: Aggression (2), Agitation (5), Morose (2), and Somnolence (6). Five of the
14 cases included at least 1 event considered serious. Somnolence was considered serious in 4 cases and Agitation was serious in 1 case. In all of the serious cases, the action taken with gabapentin was unknown but all of the patients recovered. In each of the cases of Aggression and Agitation reported from Japan, patients (age range, 3 to 13 years) were taking gabapentin for the treatment of epilepsy for an unknown period of time and at an unknown dose; further, no medical history or concomitant medications was provided. In all but 1 case [redacted] of nonserious

Agitation), the event resolved after discontinuation of gabapentin treatment. Based upon event resolution after drug discontinuation, a contributory role of is likely.

The information provided in Case [redacted] was limited and did not allow for a reasonable medical evaluation. The 16-year-old male patient described in this case experienced nonserious Depression, Aggression, and Hostility after being treated with gabapentin for headache. Action taken with gabapentin and outcome were unknown.

Aggression was also reported in 6 paediatric cases in the most recent PSUR (01 February 2005 through 31 March 2008). The investigator's brochure (March 2008) indicates that gabapentin use in paediatric patients with epilepsy aged 3 to 12 years is associated with the occurrence of Nervous System Disorders, the most significant of which could be classified as emotional lability, hostility including aggressive behaviours, though disorders including concentration problems, and hyperkinesia (primarily restlessness and hyperactivity). The events of hostility, confusion and emotional lability, depression, anxiety, nervousness, and abnormal thinking are included in the Summary of Product Characteristics (SPC) Section 4.8 Undesirable effects, although these effects are not listed as specific to paediatric patients. However, the following was included in SPC Section 4.8: Additionally, in clinical studies in children, aggressive behaviour and hyperkinesias were reported commonly. A review of post-marketing cases of Agression in children did not reveal any new or untoward information.

Six cases reported Drug exposure during pregnancy in the post-PSUR period from
01 April 2008 through 31 August 2009. All involved infants whose mothers who had been taking gabapentin for treatment of epilepsy; 5 of the 6 cases were exposed to gabapentin for the entire gestational period. The other infant was exposed to gabapentin for the first 2 months of gestation. Of the 6 infants, 2 died in utero. Of the remaining, 3 were considered healthy although 2 of these had some transitory problems as neonates (eg, drug withdrawal syndrome, feeding difficulties). The remaining was a 2-year-old female who had fetal growth retardation and permanent developmental delays at the time of the repot; however, it was considered unlikely that gabapentin had played a contributing role. It should be noted that the known risk of birth defects in the offspring of mothers treated with an antiepileptic medicinal product is included in the product labelling. It is not possible to differentiate whether an observed developmental delay is caused by genetic, social factors, maternal epilepsy, or the antiepilepsy therapy.

3. Discussion on clinical aspects and conclusion

The MAH Pfizer has submitted the report of 13 paediatric studies of gabapentin, and a critical expert overview.

In the critical expert overview, a safety review was made, which covered a period from the International Birth Date (05 February 1993) through 31 August 2009. In the review of the available data from scientific literature and the Pfizer safety database it was concluded, by MAH that, the adverse events were consistent with those listed in the SPC and that change to the SPC are not warranted at this time.

The efficacy results of the submitted studies supports the paediatric indication of gabapentin approved, and no new indication e supported by these studies.

The safety findings of the submitted studies are in line with the known safety profile of gabapentin, from the presented information no new safety signals arise.

According with the data of the A Single-Dose Study of Gabapentin Syrup (CI-945) Pharmacokinetics in Healthy Infants and Children (Protocol 945-296) paediatric subjects between 1 month and 48 month achieved approximately 30% lower exposure (AUC) than that observed in those older than 5 years, Cmax is lower and the clearance per body weight is higher in younger children. This study supports that pharmacokinetic in children less than 48 months is different that in children older than 5 years. On the other hand the studies:

- Study 945-305/405 A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study in Paediatric Patients Aged 1 Month to 36 Months With Refractory Partial Seizures (report)
- Study 945-301/401 Open-Label, Safety Study of Gabapentin as Adjunct Therapy in Children Aged 1 Month Through 4 Years With Seizures Uncontrolled by Current Anticonvulsant Drugs (protocol)

in which was used a dose of gabapentin of 40 mg/Kg/day in paediatric patients aged 1 month to 4 years, gabapentin was well tolerated and no new safety signals arise.

In conclusion although gabapentin is not licensed for children younger than 6 years, this pharmacokinetic information should be to include in SmPC, in section 5.2 Pharmacokinetic properties, because this information may be of value to prescribers.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

Based on the data submitted, SmPC changes are proposed in section 5.2.

Gabapentin pharmacokinetics in children were determined in 50 healthy subjects between the ages of 1 month and 12 years. In general, plasma gabapentin concentrations in children > 5 years of age are similar to those in adults when dosed on an mg/kg basis.

We propose to add:

In a pharmacokinetic study in 24 healthy paediatric subjects aged between 1 month and 48 months, an approximately 30% lower exposure (AUC), lower Cmax **and higher** clearance per body weight have been observed in comparison to available reported data in children older than 5 years.

The applicant is requested to submit a Type IB variation to update the SmPC in line with the above work-sharing recommendations by 01.03.2012.

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

MAH: Pfizer Ltd. UK

Invented name of the medicinal product(s): Neurontin

Pharmaceutical form(s) and strength(s): 100, 300, and 400 mg capsules, hard

600 and 800 mg tablets, film coated