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pattern of mean performance for these scores as showing improvement in the placebo group, and worsening in the levetiracetam group (Clinical Overview, pg 29).

Reviewer comment: *The finding of a statistically significant increase in the risk of aggressive behavior in levetiracetam-treated patients compared to placebo is consistent with the adverse event reports of aggressive behavior.*

The sponsor noted that the CBCL scores indicated that subjects who entered and were assessed in long-term study N01148 did not experience a worsening, on average, in their behavioral or emotional functioning (Clinical Overview, pg. 29).

The sponsor noted that for some testing, the results during open-label treatment (N01148) appeared to show somewhat different trends than those seen during the double-blind, placebo-controlled study (N01103). For instance, for the CBCL Aggressive Behavior, Externalizing Syndromes, and Total Problems scores, the levetiracetam-treated patients showed a statistically significant worsening compared to the placebo-treated subjects, during double-blind treatment. UCB noted that this worsening largely resolved during subsequent open-label treatment (Clinical Overview, pg. 30).

The sponsor noted that the slight worsening seen in levetiracetam -treated subjects from N01103 and N159 for Externalizing Behavior scores (captured with the CBCL and with the CHQ-PF50) "is consistent with the safety profile described in the drug label."

5.5.8 Psychiatric Adverse Events: Reviewer Conclusions

A number of factors are supportive of a causal relationship between the psychiatric adverse events and levetiracetam treatment. These are listed below.

1. ***Strength of Association:*** *In the placebo-controlled studies, the rate of psychiatric adverse events among levetiracetam-treated patients was higher than that in patients receiving placebo.*

2. ***Consistency Between Studies:*** *The elevation in adverse events compared to placebo was observed across placebo-controlled studies, and across neuropsychological testing.*

3. ***Consistency Between Age Groups:*** *Psychiatric adverse events were also observed in the adult development program for levetiracetam.*

4. ***Clinical Relevancy of Symptoms****: Behavioral and psychiatric adverse effects with levetiracetam are apparently known within the community of neurologists and other providers familiar with AED treatment, as judged by the number of case reports and other publications on the topic.*

If not done previously, a search of the AERS database may be helpful in further understanding the course and extent of psychiatric events during treatment with levetiracetam. However, I believe there is already sufficient evidence within the

levetiracetam development program to establish a causal link. One question the AERS analysis may be able to address is whether levetiracetam is associated with more psychiatric abnormalities than other anti-epileptic drugs.

The neuropsychiatric testing performed throughout the levetiracetam pediatric development program provided some reassurance that overall development is not harmed by levetiracetam treatment. However, if approved these issues should continued to be monitored in the post-marketing period.

5.6 Laboratory Data

5.6.1 Laboratory Data Collection

In patients aged 4 Years to 16 Years (NO1103), samples for laboratory evaluation were collected at the fist and sixth study visit. Laboratory testing was performed by a central laboratory.

5.6.2 Laboratory Data Results

UCB stated that in the 1 Month to <4 Years cohort, no "clinically relevant differences from Baseline" were noted in hematology laboratory parameters.

Reviewer comment: *The primary concern with laboratory values in the levetiracetam pediatric patients is thrombocytopenia. The Office of Drug Safety is currently reviewing cases of thrombocytopenia with levetiracetam treatment in the AERs database. In the pediatric levetiracetam development program, the data was mixed. The sponsor asserted that no trends of continuing decrease of platelet count, lymphocyte count, or eosinophil count over time by analysis interval were observed "(Clinical Overview, pg. 26). However, two subjects had TEAEs of platelet count decreased and one subject discontinued the study due to an TEAE of thrombocytopenia. During open-label, long-term levetiracetam treatment, the sponsor stated that there was a statistically significant decrease from Baseline in platelet count. However, during double-blind treatment, mean platelet count was essentially unchanged from Baseline in the levetiracetam group, while the placebo group showed a decrease after 5 days of treatment.*

Reviewer comment: *Given the short placebo-controlled phase for patients aged 1 Month to 4 Years (6 days), the longer-term, open-label data are likely more relevant in assessing laboratory values over time.*

In the 4 Years to 16 Years cohort, the sponsor stated that there were "very few" possibly clinically significant (PCS) hematology values or hematology-related TEAEs reported in the 4 Years to 16 Years cohort, and that "Overall, none of the subjects had treatment-emergent PCS platelet count values" (Clinical Overview, pg. 26).

In both placebo-controlled studies (N01009 and N01103), the sponsor reported that there were no relevant differences between levetiracetam and placebo patients in hematological values reported as a TEAE (specifically, platelet count decreased). In N01103, two subjects (6.1%) in the placebo group and five subjects (8.6%) in the levetiracetam group had a high eosinophil count values that met PCS criteria. UCB noted that both levetiracetam subjects and one placebo subject with PCS high eosinophil counts also had TEAEs of rash, and that an allergic reaction could have contributed to the (Clinical Overview, pg. 27).

In both age pools, UCB reported that there were no clinically relevant changes from Baseline for all blood chemistry parameters during levetiracetam treatment. The sponsor noted that in the 1 Month to <4 Years cohort, 0.7% of subjects had PCS AST "too high", 1.3% of subjects had PCS ALT "too high", and 5.1% of subjects had PCS GGT "too high" during the Overall Treatment Phase. Treatment-emergent AEs related to liver function test results included: 1.2% of subjects each with ALT increased and AST increased; and 0.6% of subjects each with GGT /transaminases increased.

In placebo-controlled studies N01009 (aged 1 Month to <4 Years) and N01103 (aged 4 Years to 16 Years), UCB asserted that "no general trend in blood chemistry changes related to levetiracetam exposure could be detected" (Clinical Overview, pg. 27).

Reviewer comment: *I reviewed the laboratory data within placebo-controlled studies NO1009 and NO1103 and found the sponsor's statement above to be overall correct.*

5.7 Vital Sign Data

5.7.1 1 Month to <4 Years

In placebo-control study NO1109 (patients aged 1 Month to <4 Years), vital sign data was collected at baseline and throughout the inpatient placebo-controlled period.

In the 1 Month to <4 Years cohort during open-label treatment, the sponsor stated that the 95% CI around the median change from Baseline to the Last Value in weight percentile did not exclude zero. The sponsor stated, however, that there was a statistically significant decrease from Baseline in height percentile (mean [median] change from Baseline: -4.00 [-1.58], 95% CI: -5.20 to -0.10). UCB commented that this suggests that levetiracetam-treated the children "fell slightly" behind the growth curve in terms of height at the Last Value on Treatment (Clinical Overview, pg. 27).

Reviewer comment: *I was unable to locate other significant sponsor commentary on the apparent decrease in growth in levetiracetam-treated children, as noted above. The sponsor should be asked to assess this in a more thorough manner. Should levetiracetam be approved, consideration should be given to requesting that the sponsor monitor patient height in the post-marketing period. This could be done through a cohort study within a medical records database.*

Pooled placebo-controlled and open-label data: A higher proportion of subjects in the 1 Month to <4 Years cohort had PCS heart rate values too low/decreased (27.5%), compared to PCS heart rate values too high/increased (7.2%). A higher proportion of subjects had PCS systolic blood pressure too high/increased (12.1%) compared to 7.3% of subjects with PCS systolic blood pressure too low/decreased. UCB stated that there was "overall….there was no correlation observed between PCS heart rate too low/decreased, and systolic and diastolic blood pressure too high/increased" (Clinical Overview, pg. 27).

Placebo-controlled data: During N01009, a higher proportion of subjects in the levetiracetam group, compared to the placebo group, had PCS diastolic blood pressure too high/increased (16.7% vs. 1.8% of subjects, respectively) and PCS heart rate too low/decreased (21.7% vs. 12.5% of subjects, respectively).

Reviewer comment: *In Study N01009, Possibly Clinically Significant (PCS) criteria for diastolic blood pressure was defined as:*

- For 1 m to < 12 m: < 40 mmHg and a decrease of > 15 mmHg from baseline or > 60 mmHg and an increase of > 20 mmHg from baseline

- For 12 m to < 6 y: < 45 mmHg and a decrease of > 15 mmHg from baseline or > 80 mmHg and an increase of > 20 mmHg from baseline

The sponsor stated that no correlation was observed between increase in diastolic blood pressure and decrease in heart rate (Clinical Overview, pg. 27). The sponsor also noted that:

> "The subjects were evaluated each day during the hospitalization for the study and the changes were not persistent or uniform each day. Four subjects in the LEV group had more than one post-baseline PCS diastolic blood pressure value too high, however, a majority of these subjects had varied extents of elevated diastolic blood pressure values during screening prior to baseline. None of the PCS diastolic blood pressure values were reported as an AE."

Reviewer comment: *The sponsor did not comment further on the substantial difference in patients with PCS increases in diastolic blood pressure (16.7% in levetiracetam patients, 1.8% in placebo patients) and decreased heart rate (21.7% in levetiracetam patients, 12.5% in placebo).*

For the increase in diastolic blood pressure, in Study N01009 the actual number of patients affected was 10 in the levetiracetam-treatment group (17%) and 1 in the placebo-treatment group (1.8%). Five levetiracetam-treated patients had a diastolic blood pressure increase of greater than 20 mmHg, compared to one placebo-treated patient.

When the average diastolic blood pressure for the levetiracetam- and placebo-treated patients within Study N01009 were compared by hospital day[29], the results were the following (figures taken from Table 14.3.6:1, Study N01009 Report, pg. 583):

Hospital Day	***Levetiracetam-Treated Patients***	***Placebo-Treated Patients***
1	*55.9*	*59.7*
2	*60.6*	*62.1*
3	*58.3*	*59.6*
4	*57.2*	*58.0*
5	*58.0*	*59.9*
6	*58.3*	*59.7*

As such, although there was an imbalance in the number of patients meeting the PCS criteria for diastolic blood pressure increased, there was not an imbalance by treatment group in the average daily diastolic blood pressure.

In the older cohort of patients (aged 4 to 16 years), during the placebo-controlled trial (N01103) 1 levetiracetam-treated patient (1.6% out of a total of 46 levetiracetam patients) and 1 placebo-treated patient (2.9% of a total of 34 placebo patients) were classified as PCS diastolic blood pressure too high/increased.

An increase in diastolic blood pressure is not described in the adult labeling for levetiracetam.

Based on the magnitude of the disparity (17% versus 2%), the increase in the number of patients with PCS diastolic blood pressure increased in the levetiracetam compared to placebo patients in the 1 Month to <4 Year age group is concerning and should be described in labeling. However, a number of the factors just discussed, such as the lack of replication in the other age groups and the equivalent overall diastolic blood pressures in the 1 Month to <4 Years age group, mitigate this concern somewhat.

5.7.2 4 Years to 16 Years

In placebo-controlled study N01103 (patients aged 4 years to 16 years), vital signs were collected from patients at all study visits.

In the 4 Years to 16 Years Pool, the sponsor stated there were no "relevant" changes from Baseline during double-blind treatment for all vital sign parameters. During levetiracetam treatment, the most frequently reported PCS vital sign parameters were weight increase, weight decrease, and diastolic blood pressure too low/decreased. UCB noted that only one vital sign-related TEAE (weight decreased) was reported in the 4 Years to 16 Years pool. The percentage of subjects with abnormal vital sign values or

[29] The placebo-controlled period from this study was 6 days inpatient hospitalization.

5. ***Increased Diastolic Blood Pressure:*** Based on the magnitude of the disparity (17% versus 2%), the increase in the number of patients with PCS diastolic blood pressure increased in the levetiracetam compared to placebo patients in the 1 Month to <4 Year age group is concerning and should be described in labeling. However, a number of factors, such as the lack of replication in the other age groups and the equivalent overall diastolic blood pressures in the 1 Month to <4 Years age group, mitigate this concern somewhat.

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7. ATTACHMENTS

7.1 All Clinical Studies in Pediatric Patients treated with Levetiracetam

(Taken from Sponsor Table 2.7.4.1, Summary of Clinical Safety, pg. 7.)

Table 2.7.4:1 Clinical Studies in Pediatric Population with Levetiracetam

Study Number/ Design	Population	Objective	Dosage and Dosage Form	Duration of Study/ Status
Clinical Pharmacology Studies in Pediatric Epileptic Subjects with Partial Onset Seizures				
N01052 Multicenter, Open-Label, Single-Dose, PK	Pediatric epileptic subjects with refractory partial onset seizures (1 month to <4 years) (N=13)	Pharmacokinetic evaluation in infants and children aged <4 years	20 mg/kg Oral solution	3 weeks/ Completed
N01010 Multicenter, Open-Label, PK	Pediatric epileptic subjects with refractory partial onset seizures (4 to 12 years) (N=21)	Pharmacokinetic linearity and bidirectional evaluation of 2 AEDs and LEV	20 to 40 to 60 mg/kg/day Tablets	12 weeks/ Completed
N151 Multicenter, Open-Label, PK	Pediatric epileptic subjects with partial onset seizures (5 to 12 years) (N=24)	Pharmacokinetic, efficacy, and safety	10 to 40 mg/kg/day Tablets	22 weeks/ Completed
Placebo-Controlled Studies in Pediatric Epileptic Subjects with Partial Onset Seizures				
N01009 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Add-on	Pediatric epileptic subjects with refractory partial onset seizures (1 month to <4 years) (N=116)	Efficacy and safety	20 mg/kg/day to 50 mg/kg/day Oral solution	34 days/ Completed
N159 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Add-on	Pediatric epileptic subjects with refractory partial onset seizures (4 to 16 years) (N=216)[a]	Efficacy and safety	20 to 40 to 60 mg/kg/day Tablets	28 weeks/ Completed
N01103 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Add-on	Pediatric epileptic subjects (4 to 16 years) (N=99)	Monitor cognitive and neuropsychiatric effects and safety of LEV	20 to 60 mg/kg/day Tablets or Oral solution	19 weeks/ Completed

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