

# Suicidality and Anti-epileptic Drugs: Status of Clinical Trial Data Analysis

Evelyn Mentari, MD, MS  
Division of Neurology Products

# Background

- The Division of Neurology Products is analyzing the potential association between anti-epileptic drugs (AEDs) and suicidal thinking and behavior in placebo-controlled trials
  - The division's analysis is independent of the post-pediatric exclusivity post-marketing adverse event review just presented
- Post-marketing cases of suicidal thinking and behavior are difficult to interpret
  - Known limitations of post-marketing data
  - Patients with epilepsy (and other illnesses for which AEDs are being prescribed) have increased risk of suicide

# Background

- An AED sponsor approached the Division with concern of a suicidality signal in their controlled clinical trial database
- In response, the Division initiated an analysis of suicidality events in controlled clinical trial databases of all AEDS
- Sponsors were asked (in March, 2005) to provide data from their placebo-controlled trial experience
- Division will conduct meta-analysis of all data

# Background

- Standardized approach is based on previous FDA analysis of suicidality in children and adolescents treated with antidepressants
  - In this analysis, pediatric patients treated with antidepressants were found to have an increased risk of suicidality compared to those treated with placebo

# Suicidality Analysis

- Analysis includes parallel-arm, placebo-controlled trials with at least 20 subjects in each treatment arm
- A search for events related to suicidal behavior or possibly related to suicidal behavior was performed by the sponsors, using search terms specified by FDA

# Suicidality Events: Search Terms

- Preferred terms with text strings “suic” or “overdos,” including all events coded as “accidental overdose”
- Verbatim terms with the text strings: “attempt”, “cut”, “gas”, “hang”, “hung”, “jump”, “mutilat-”, “overdos-”, “self damag-”, “self harm”, “self inflict”, “self injur-”, “shoot”, “slash”, “suic-”, “poison”, “asphyxiation”, “suffocation”, “firearm”; events were screened for false positives
- All deaths and other serious adverse events (SAEs)
- All adverse events coded as “accidental injury”

# Suicidality Analysis

- After events were found using this search strategy, structured narratives were prepared
- Based on these narratives, events were classified into 7 categories
  - Classification was done by raters blinded to treatment

# Suicidality Event Classification

1. Completed suicide
2. Suicide attempt
3. Preparatory acts toward imminent suicidal behavior
4. Suicidal ideation
5. Self-injurious behavior, intent unknown
6. Not enough information, fatal
7. Not enough information, non-fatal

# Drugs To Be Evaluated

- Pregabalin (Lyrica)
- Valproic acid (Depakote)
- Gabapentin (Neurontin)
- Lamotrigine (Lamictal)
- Tiagabine (Gabitril)
- Zonisamide (Zonegran)
- Oxcarbazepine (Trileptal)
- Levetiracetam (Keppra)
- Carbamazepine (Carbatrol)
- Topiramate (Topamax)
- Felbamate (Felbatol)

# Status of Submissions

- Nine sponsors have submitted data
- Data received includes 36,290 subjects from 170 trials
- Oxcarbazepine (Trileptal) data has been submitted

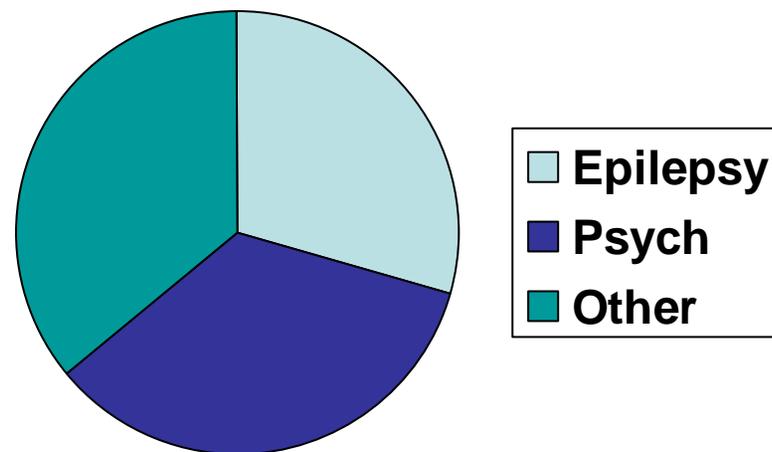
# Nine Submissions Received: Subject Age Distribution

- 36,290 subjects
- 170 trials

Age	# Subjects (%)
<5 y	135 (0.3%)
5-11 y	1,173 (3.2%)
12-17 y	771 (2.1%)
18-24 y	3,212 (8.8%)
25-64 y	26,021 (71.7%)
>64 y	4990 (13.7%)

# Nine Submissions Received: Trial Indication Distribution

- Epilepsy 29.4%
- Psychiatric Diagnoses 34.6% (e.g., Bipolar Disorder, Anxiety Disorders)
- Other 34.6% (e.g., Neuropathic Pain, Chronic Pain)



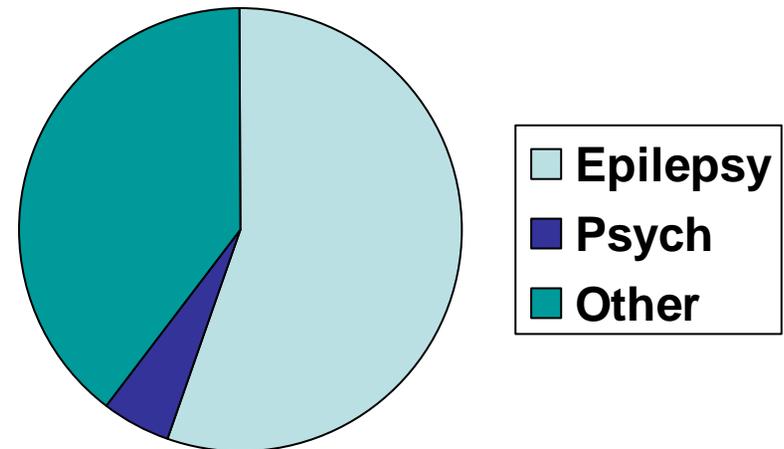
# Oxcarbazepine (Trileptal) Submission

- 12 trials
- Total of 2370 subjects
- 1470 subjects treated with Trileptal

Age	# Subjects (%)
<5 y	18 (0.7%)
5-11 y	193 (8.1%)
12-17 y	227 (9.6%)
18-24 y	189 (8.0%)
25-64 y	1470 (62.0%)
>64 y	273 (11.5%)

# Oxcarbazepine (Trileptal): Trial Indication Distribution

- Epilepsy 55.3%
- Psychiatric Diagnoses 4.9% (e.g., Bipolar Disorder)
- Other 39.8% (e.g., Neuropathic Pain, Chronic Pain)



# Future Plans

- Meta-analysis will proceed once all sponsor submissions are received
- Depending on results of analysis, data may be presented at an advisory committee meeting and/or regulatory action may be indicated