

Pediatric Focused Safety Review: Keppra[®] (Levetiracetam)

**Pediatric Advisory Committee Meeting
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Outline

- Background Information
- Pediatric Labeling Changes
- Pediatric Studies
- Drug Use Trends
- Adverse Events
- Summary

Background Drug Information: Keppra® (Levetiracetam)

- **Original Market approval:** 1999
- **Therapeutic Category:** Antiepileptic
- **Sponsor:** UBC Inc.
- **Indications (oral IR tablet/solution/intravenous injection):**
 1. Adjunctive treatment of partial onset seizures (**adult and pediatric 1 month and older**)
 2. Adjunctive treatment of myoclonic seizures in patients with juvenile myoclonic epilepsy (**adult and pediatric 12 years and older**)
 3. Adjunctive treatment of primary generalized tonic clonic seizures (**adult and pediatric 6 years and older**)
- **Indications (oral XR tablet):**
 1. Adjunctive treatment of partial onset seizures (**adult and pediatric 12 years and older**)



Pediatric Labeling

Keppra[®] (Levetiracetam Injection for Intravenous Use)

- **Adult approval: July 31, 2006**
- **Pediatric labeling: October 30, 2014***
- **Pediatric Use:**

Safety and effectiveness in pediatric patients have been established based on PK data in adults and children using parenteral levetiracetam and efficacy and safety data in controlled pediatric studies using oral levetiracetam.

*Basis for current review.

Pediatric Labeling

Keppra[®] (Levetiracetam XR tablets)

- **Adult approval: September 12, 2008**
- **Pediatric labeling: August 1, 2014***
- **Pediatric Use:**

Safety and effectiveness in pediatric patients ≥ 12 years of age have been established based on pharmacokinetic (PK) data in adults and adolescents using levetiracetam XR and efficacy and safety data in controlled pediatric studies using immediate-release levetiracetam.

- **Dosing:**

Same as in adults

* Basis for current review.

Adverse Events: Keppra[®] (Levetiracetam)

Warning and Precautions (Section 5):

- Behavioral abnormalities and psychotic symptoms
- Suicidal behavior and ideation
- Somnolence/fatigue
- Anaphylaxis/angioedema
- Increase diastolic blood pressure in patients younger than 4 years

Adverse Events (Section 6):

- **Adults**
 - Somnolence, asthenia, infection, and dizziness
- **Pediatric patients**
 - Fatigue, aggression, nasal congestion, decreased appetite, and irritability

Drug Utilization: Levetiracetam

Nationally Estimated Number of Patients with a Dispensed Prescription for Levetiracetam by Patient Age from U.S. Outpatient Retail Pharmacies, August 2014 through December 2016

	Patients (N)	Share %
Levetiracetam (all forms) Total Patients	2,378,146	100.0%
Levetiracetam Immediate Release (solution/tablet) Oral	2,282,064	96.0%
0 - 16 years	346,507	15.2%
17 years and older	1,933,379	84.7%
Levetiracetam Extended Release Oral	154,983	6.5%
0 - 16 years	25,279	16.3%
17 years and older	131,096	84.6%

Source: QuintilesIMS, Total Patient Tracker™. Aug 2014 – Dec 2016. Extracted April 2017.



Drug Utilization: Levetiracetam

Nationally Estimated Number of Patients with Hospital Discharge Billing for Levetiracetam from U.S. Non-Federal Hospitals, August 2014 through December 2016

	Patients (N)	Share %
Levetiracetam (all forms) Total Patients	2,413,986	100%
Levetiracetam Oral	1,619,653	67%
0 - 16 years	99,564	6%
17 years and older	1,520,818	94%
Levetiracetam Injection	1,009,962	42%
0 - 16 years	79,011	8%
17 years and older	931,246	92%
Levetiracetam Formulation Unspecified	698,604	29%

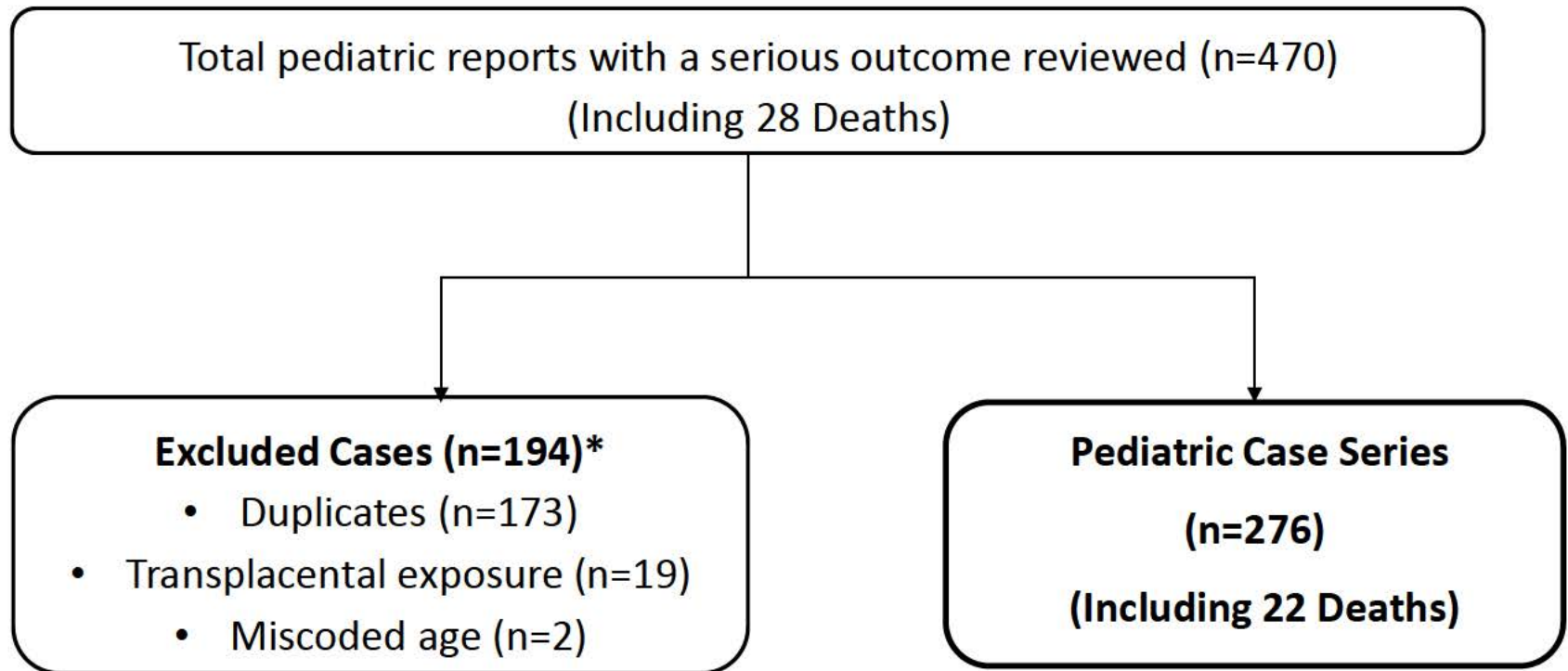
Source: QuintilesIMS, Hospital Visit Analyzer (HVA). Aug 2014 – Dec 2016. Extracted April 2017

Total Number of FAERS Reports* with Levetiracetam (May 31, 2013- December 31, 2016)

	All reports (US)	Serious (US) [†]	Death (US)
Adults (≥ 17 yrs.)	6,194 (2,497)	5,397 (1,828)	629 (269)
Pediatrics (0-<17 yrs.)	1,505 (691)	1,246 (470)	86 (28)

*May include duplicates and transplacental exposures, and have not been assessed for causality
[†]For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

Selection of Serious Pediatric FAERS Cases Levetiracetam (Keppra®)



*Reviewed and excluded for stated reasons.

Summary of Serious Adverse Event Cases (n=276)

- **Adverse events consistent with known risks described in the labeling (reported in ≥ 5 cases) include:**
 - behavioral abnormalities and psychotic symptoms
 - somnolence and fatigue
 - gastrointestinal adverse events
 - dermatological and allergic reactions
 - movement disorders
 - sleep disorders
 - coordination difficulties or dizziness
 - hematologic abnormalities
 - suicidal behavior and ideation

Summary of Serious Adverse Event Cases

Fatal Adverse Events (n=22)



- **22 pediatric patients had a fatal outcome**
 - No case provided evidence of a causal association with levetiracetam.
 - All cases reported alternative etiologies and did not provide adequate information for causality assessment, and 12 out of 22 cases reported concomitant use of other antiepileptic drugs (AEDs).
- **Fatal Adverse Events (n=22)**
 - Seizures (n=5)
 - Sudden unexpected death in epilepsy (SUDEP) (n=3)
 - Complications from hypoxic ischemic encephalopathy (HIE) (n=10)
 - Respiratory failure (n=3)
 - Meningoencephalitis (n=1)

Summary of Serious Adverse Event Cases (n=276)

- **Nonfatal Serious Adverse Events:**
 - Unlabeled events* were consistent with the underlying disease or indication for use; events reported in ≥ 5 cases include:
 - Seizures (adverse event confounded by indication)
 - Drug ineffective, condition aggravated
 - Product substitution/product use/product quality issue
 - Off label use; drug administered to patient of inappropriate age

* Unlabeled events are underlined

Serious Unlabeled Events of Interest

- Cardiovascular (n=4)
 - Cardiac arrest after an intentional overdose involving multiple drugs (n=2)
 - Hypotension after an intentional overdose (n=1)
 - Increased premature ventricular contractions (PVCs) in a neonate with pre-existing PVCs (n=1)
- Rhabdomyolysis (n=1)
 - Following levetiracetam administration for tonic-clonic seizures
- Encephalopathy (n=1)
 - Patient presenting with renal failure and metabolic acidosis on levetiracetam
- Neurophysiologic abnormalities (n=1)
 - During craniotomy for a tumor resection while receiving levetiracetam



Summary Pediatric Focused Safety Review: Keppra® (Levetiracetam)

- In conclusion, most cases included known adverse events in patients with underlying medical conditions
- No new safety signal was identified
- Plan to monitor for cardiovascular adverse events, rhabdomyolysis, and encephalopathy in all patient populations
- FDA recommends continuing ongoing surveillance
- Does the Committee concur?



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