Pediatric Focused Safety Review: Seroquel® (quetiapine fumarate) Seroquel XR® (quetiapine fumarate, extended release)
Pediatric Advisory Committee Meeting
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Outline

- Background Information
- Relevant Labeling
- Drug Use Trends
- Safety
- Summary

Background Drug Information Seroquel® and Seroquel XR® (quetiapine fumarate)

- **Drug:** Seroquel® and Seroquel XR®
- **Formulations:**
  - 25, 50, 100, 200, 300 and 400 mg tablets
  - 50, 150, 200, 300 and 400 mg extended release tablets
- **Sponsor:** AstraZeneca Pharmaceuticals LP
- **Original Market Approval:** September 26, 1997
- **Pediatric Labeling Changes:** December 2, 2009 and April 30, 2013
- **Therapeutic Category: Atypical antipsychotic**
- **Postmarketing Requirements: None**
- **Prior Pediatric Advisory Committee Review:** September 11, 2012

Background Drug Information Seroquel® and Seroquel XR® (quetiapine fumarate)

- **Indications (Seroquel):**
  - Schizophrenia 13 years of age and older
  - Bipolar disorder manic episodes 10 years of age and older
  - Bipolar disorder, depressive episodes in adults

- **Indications (Seroquel XR):**
  - Schizophrenia 13 years of age and older
  - Bipolar disorder, manic and mixed episodes 10 years of age and older
  - Bipolar disorder, depressive episodes in adults
  - Major depressive disorder in adults

Pediatric Studies, continued Seroquel® and Seroquel XR® (quetiapine fumarate)

- The efficacy and safety of Seroquel® and Seroquel XR® in the treatment of schizophrenia in adolescents aged 13 to 17 years is supported by one 6-week, double-blind, placebo-controlled trial with Seroquel®
- The efficacy and safety of Seroquel® and Seroquel XR® in the treatment of bipolar mania in children and adolescents ages 10 to 17 years is supported by one 3-week, double-blind, placebo controlled trial with Seroquel®
- The efficacy and safety of Seroquel® and Seroquel XR® in the treatment of bipolar depression was not established in children and adolescents ages 10 to 17 years is supported by one 8-week, double-blind, placebo controlled trial with Seroquel XR®*

*Study and labeling change which initiated the current PAC review

Relevant Labeling, continued Seroquel® and Seroquel XR® (quetiapine fumarate)

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. SEROQUEL (XR) is not approved for elderly patients with dementia-related psychosis**

Suicidal Thoughts and Behaviors

- **Increased risk of suicidal thoughts and behavior in children, adolescents and young adults taking antidepressants**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors**

Relevant Labeling, continued Seroquel® and Seroquel XR® (quetiapine fumarate)

2 DOSAGE AND ADMINISTRATION

	Indication	Initial Dose	Recommended Dose	Maximum Dose
Seroquel®	Schizophrenia 13 to 17 years	25 mg twice daily	400-800 mg/day	800 mg/day
	Bipolar Mania 10 to 17 years Monotherapy	25 mg twice daily	400-600 mg/day	600 mg/day
Seroquel XR®	Schizophrenia 13 to 17 years	50 mg/day	400-800 mg/day	800 mg/day
	Bipolar I Disorder Manic Acute, Monotherapy 10 to 17 years	50 mg/day	400-600 mg/day	600 mg/day

Relevant Labeling, continued Seroquel® and Seroquel XR® (quetiapine fumarate)

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis
5.2 Suicidal Thoughts and Behaviors in Adolescents and Young Adults
5.3 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis
5.4 Neuroleptic Malignant Syndrome (NMS)
5.5 Metabolic Changes – Hyperglycemia and Weight Gain
5.6 Tardive Dyskinesia
5.7 Hypotension
5.8 Increases in Blood Pressure (Children and Adolescents)
5.9 Leukopenia, Neutropenia and Agranulocytosis

Relevant Labeling, continued Seroquel® and Seroquel XR® (quetiapine fumarate)

5 WARNINGS AND PRECAUTIONS (continued)

5.10 Cataracts
5.11 QT Prolongation
5.12 Seizures
5.13 Hypothyroidism
5.14 Hyperprolactinemia
5.15 Potential for Cognitive and Motor Impairment
5.16 Body Temperature Regulation
5.17 Dysphagia
5.18 Discontinuation Syndrome

Relevant Labeling, continued Seroquel® and Seroquel XR® (quetiapine fumarate)

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

The most common adverse reactions observed in short-term pediatric placebo controlled trials:

- Bipolar depression: dizziness, diarrhea, fatigue and nausea
- Schizophrenia: somnolence, dizziness, dry mouth, tachycardia
- Bipolar mania: somnolence, dizziness, fatigue, increased appetite, nausea, vomiting, tachycardia, dry mouth, and weight increased

6.2 Postmarketing Experience

Anaphylactic reaction, cardiomyopathy, hyponatremia, myocarditis, nocturnal enuresis, pancreatitis, retrograde amnesia, rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)

Relevant Labeling, continued Seroquel® and Seroquel XR® (quetiapine fumarate)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Safety and effectiveness of Seroquel® and Seroquel XR® is supported by studies of Seroquel® for schizophrenia in adolescent patients 13 to 17 years of age and in bipolar mania in children and adolescent patients 10 to 17 years of age.

The effectiveness of Seroquel® and Seroquel XR® for the treatment of bipolar depression in patients under the age of 18 years has not been established.

Relevant Labeling, continued Seroquel® and Seroquel XR® (quetiapine fumarate)

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics (PK)

Some differences are noted in PK between adult and pediatric patients. When dose is adjusted for weight, the PK is lower for quetiapine in pediatric patients compared to adults, but the PK of the metabolite, norquetiapine, is similar.

14 CLINICAL STUDIES

Study data for pediatric patients 13 to 17 years of age for treatment of schizophrenia and pediatric patients 10 to 17 years of age for treatment of bipolar mania

Pediatric Drug Utilization: quetiapine (Quetiapine & Quetiapine XR)

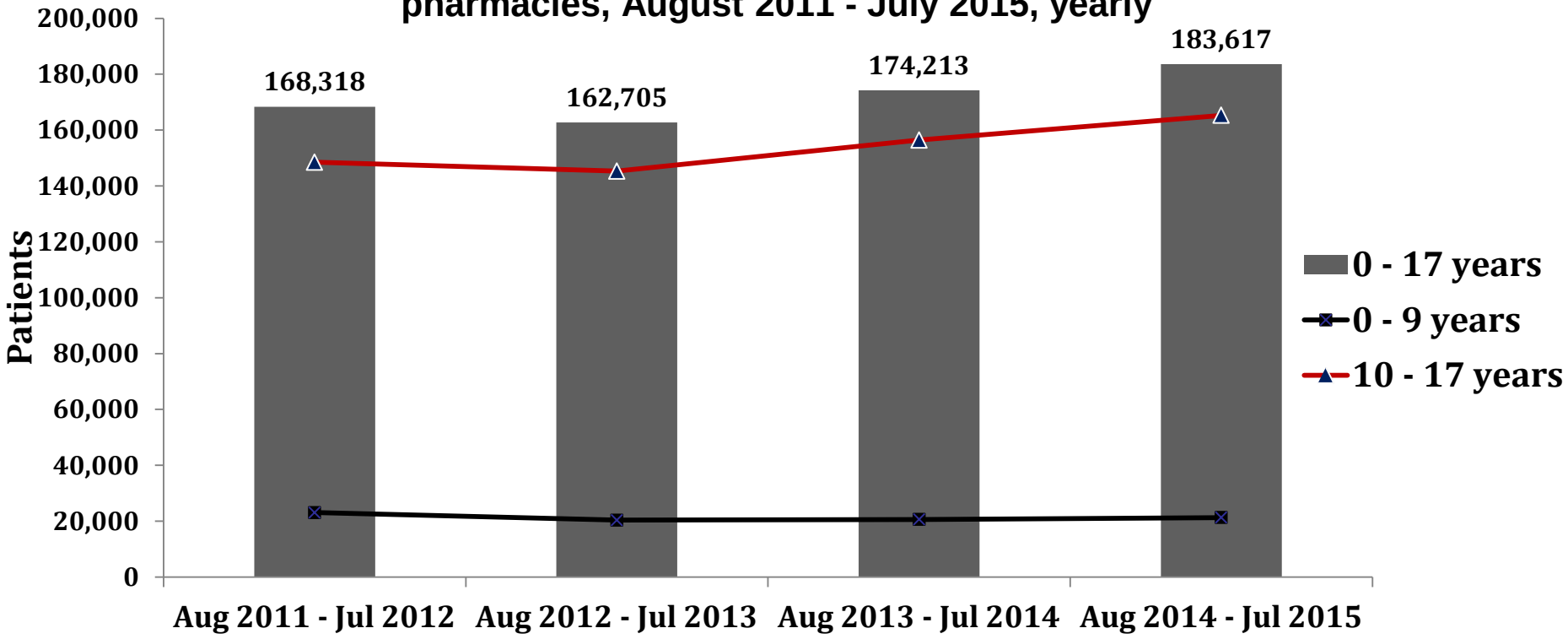
National estimates of adult and pediatric patients (0-9 and 10-17 and 18+ years) who received a quetiapine/quetiapine XR dispensed prescription from U.S. outpatient retail pharmacies, August 2011 - July 2015

	Aug 2014 - Jul 2015	
	Patients (N)	*Share %*
Grand Total	**2,784,320**	***100%***
0 - 17 years	**183,617**	***6.59%***
0 - 9 years	21,294	*11.60%*
10 - 17 years	165,282	*90.01%*
18+ years	**2,591,031**	***93.06%***
UNKNOWN AGE	**34,945**	***1.26%***

Source: IMS Health, Vector One®: Total Patient Tracker. Data extracted January 2016

Pediatric Drug Utilization: quetiapine (Quetiapine & Quetiapine XR)

National estimates of pediatric patients (0-9 and 10-17 years) who received a quetiapine/quetiapine XR dispensed prescription from U.S. outpatient retail pharmacies, August 2011 - July 2015, yearly



Source: IMS Health, Vector One®: Total Patient Tracker. Data extracted January 2016

Drug Use Data: quetiapine (Quetiapine& Quetiapine XR)

Prescriber Specialty and Diagnosis Data: Aug 2011- July 2015

Prescriber Data[1]

- Psychiatry (47%)
- Nurse Practitioner (14%)
- Pediatric specialists (less than 1%)

Diagnosis Data[2]

- 0-9 years* : Attention Deficit Disorder (ICD-9 314.0)
- 10-17 years: Affective Psychoses (ICD9 296.9)

*Drug use mentions are low for reliable national estimates of use by diagnoses.

[1]IMS Health, Health National Prescription Audit (NPA). Extracted January 2016
[2]Encuity Research, LLC,Treatment Answers with Pain™ 5. Extracted January 2016.

Total Number of Seroquel® and Seroquel XR® FAERS Reports* August 1, 2011†to July 31, 2015

	All reports (US)^	Serious (US)**	Deaths (US)
Adults (≥ 17 years)	19,495 (13,325)	12,419 (6,289)	3,103 (2,408)
Pediatrics (0 to < 17 years)	838 (403)	670 (236)	77 (42)

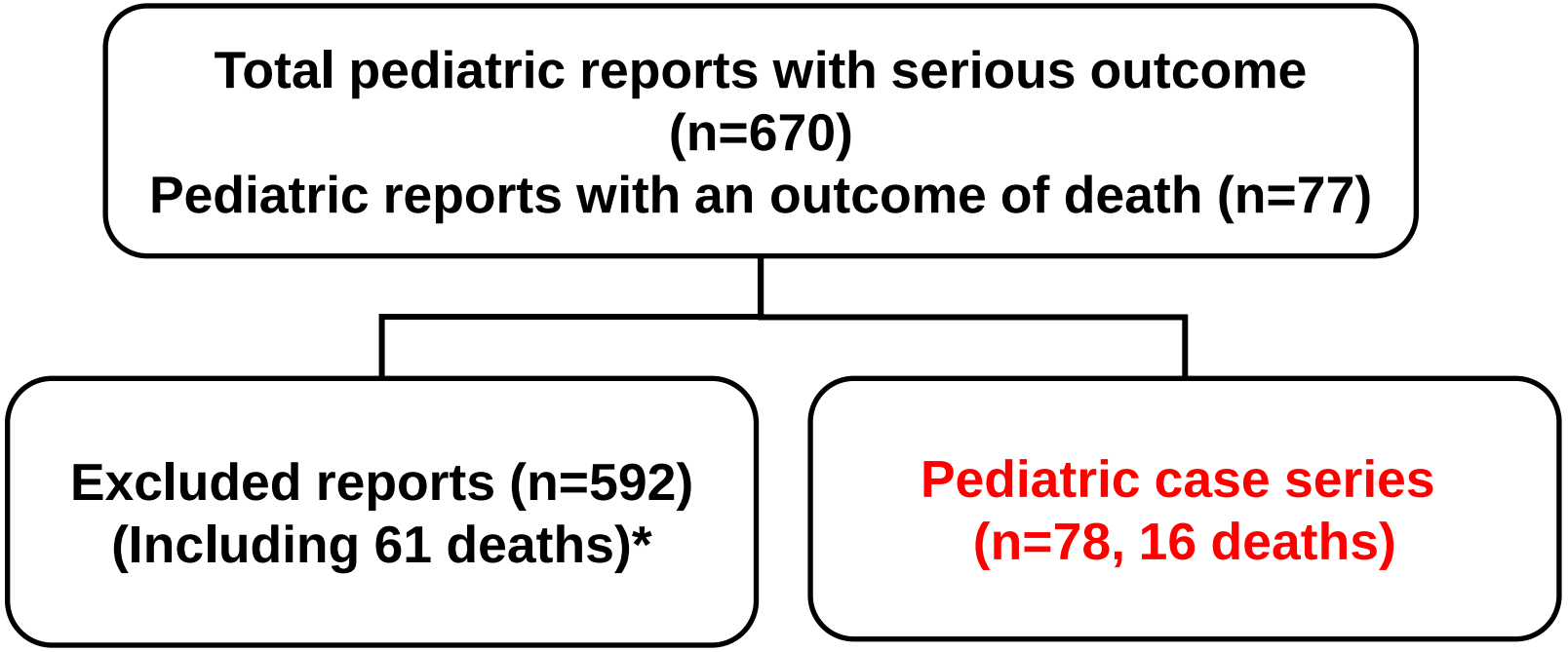
* May include duplicates and transplacental exposures and all cases may not have not been assessed for causality

† Date from last AERS search in DPV pediatric review of quetiapine fumarate dated December 2011

^ US counts in parentheses

** 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 Pediatric FAERS Cases August 1, 2011 to July 31, 2015



* Reviewed and excluded for reasons detailed on slide 18

Selection of Pediatric FAERS Cases August 1, 2011 to July 31, 2015

Excluded Cases (n = 592, including 61 deaths)

- Duplicates (n=303, including 49 deaths)
- Transplacental/Transmammary exposure reviewed separately by the Office of Pediatric Therapeutics (OPT) (n=177, including 12 deaths)
- Labeled events (n=83)
- Confounded by disease or indication (n=13)
- Product substitution/Drug ineffective (n=10)
- Lack of temporal association (n=9)
- No or non-specific adverse event reported (n=8)
- Adult (n=4)
- Alternative cause (n=5)
- Insufficient information for assessment (n=1)
- Adverse event deemed not serious (n=1)

OPT Review of Unlabeled Transplacental Adverse Events, Seroquel® and Seroquel XR® (quetiapine fumarate)—1/2010-7/2015

- Premature birth, n = 27
- No specific pattern of anomalies was determined
  - Atrial septal defect (n = 9), Pyloric stenosis (n = 6), Talipes equinovarus (n = 6), Cleft lip and palate (n = 4), Ventricular septal defect (n = 4), Pulmonary stenosis or atresia (n = 4), Miscellaneous AEs, each anomaly with 1-3 events reported (n=21)
- Given the broad spectrum of anomalies noted in FAERS, and the widespread use of Seroquel® and Seroquel®XR, the FAERS reports do not suggest a new signal of clinical concern

Characteristics of Pediatric Case Series With Seroquel® and Seroquel XR® (quetiapine fumarate) (N=78)

Age	1 month - < 2 years	2
	2- < 6 years	3
	6- <12 years	11
	12- < 17 years	62
Sex	Male	42
	Female	36
Country	United States	43
	Foreign	35

Characteristics of Pediatric Case Series With Seroquel® and Seroquel XR® (quetiapine fumarate) (N=78)

Reason for Use*	Bipolar Disorder	14
	Depression	9
	Behavior Disorder	4
	Schizophrenia/Schizophrenia, paranoid/Psychosis	3
	Suicide attempt/Suicide	3
	Affective disorder	2
	Attention Deficit/Hyperactivity Disorder (ADHD)	2
	Post-Traumatic Stress Disorder (PTSD)	2
	Single Report	14
	Unknown	25
Serious Outcome†	Death	16
	Life-threatening	16
	Hospitalized	29
	Disability	3
	Other serious	25

***** Reason for use - the information that was provided in the indication field of the MedWatch report.

† Serious adverse drug experiences per regulatory definition (CFR 314.80). Reports may have more than one outcome.

Deaths (n=16)
Seroquel® and Seroquel XR®
(quetiapine fumarate)

- Patients ages ranged from 4 to 16 years of age (median 14 years)
- Doses were reported in 5 cases: 50 mg, 200 mg, 500 mg, 900 mg and 16,000 mg
- Half of the cases were reported from literature
- Only 3 cases did not report multiple concomitant drug ingestion
  - These cases are discussed on the subsequent slide

Deaths, Continued (n=16) Seroquel® and Seroquel XR® (quetiapine fumarate)

- **15-year-old female died after ingesting 2 quetiapine tablets of unknown strength**
  - No past medical history (PMH) or concomitant medications were reported. In the emergency room (ER) her heart rate (HR) was 150/min. Upon HR stabilization she was transferred to an inpatient psychiatry unit. Six hours later she returned to the ER seizing with fixed and dilated pupils. Cardiopulmonary resuscitation failed and she died. No cause of death was reported.

- **15-year-old male with bipolar disorder died in sepsis**
  - Treated with quetiapine at 900 mg daily for an unspecified period of time
  - Neuroleptic malignant syndrome was reportedly ruled out
  - PMH, concomitant medications, and cause of death were not reported

- **14-year-old female died after potential exposure to quetiapine**
  - Concomitant medications, dose of quetiapine and cause of death were not reported

Serious Non-Fatal Unlabeled Adverse Events Seroquel® and Seroquel XR® (quetiapine fumarate) (n=62)

Psychiatric Disorders – Suicidal thoughts and behaviors (n=28)

Psychiatric Disorders – Other (n=7)

Eye Disorders (n=7)

Gastrointestinal and Hepatic Disorders (n=6)

Pulmonary/Respiratory/Vascular Disorders (n=4)

Nervous System Disorders (n=3)

Musculoskeletal Disorders (n=2)

Miscellaneous (n=5)

*Unlabeled events are underlined on subsequent slides

Non-Fatal Unlabeled Adverse Events, continued, Seroquel® and Seroquel XR® (quetiapine fumarate)

Psychiatric Disorders – Suicidal thoughts and behaviors (n=28)

- These cases reported an overdose, self-injurious behavior, suicidal ideation, or suicidal attempt. The Boxed Warning for Seroquel and Seroquel XR includes a discussion of suicidal ideation and suicidal behavior.
- Reported reasons for taking quetiapine: depressed mood (n=9), bipolar disorder (n=6), post traumatic stress disorder (PTSD) (n=2), suicide attempt (n=2), unspecified (n=5), affective disorder (n=1), Asperger's disorder (n=1), autism spectrum disorder (n=1), schizotypal personality disorder (n=1)
- The median age was 15 years old, range 7 to 16 years, equal number of females and males
- Several patients were on concomitant medications that may have contributed to the reported event

Non-Fatal Unlabeled Adverse Events, continued, Seroquel® and Seroquel XR® (quetiapine fumarate)

Psychiatric Disorders – Other (n=7)

- 7 cases reported drug abuse (n=2), tic (n=2), and one case each of mental damage, mood swings, and obsessive compulsive disorder (OCD).
- 4 cases did not report an outcome
- 3 cases reported resolution when quetiapine was stopped, with 2 of the patients reporting recurrence when quetiapine was reintroduced
- 1 of these 3 cases noted resolution of tics with lowering the dose from 600 mg to 50 mg but later reported that the tics resolved once haloperidol was added, despite increasing dose of quetiapine to 600 mg

Non-Fatal Unlabeled Adverse Events, continued, Seroquel® and Seroquel XR® (quetiapine fumarate)

Eye Disorders (n=7)

- The reported events were papilledema (n=2), "vision loss" (n=2), and one case each of astigmatism, extraocular muscle disorder and miosis
- Cases included 3 females and 4 males, median age of 15 years, range 10 months to 16 years
- The median daily dose of quetiapine was 50 mg, range 25 mg to 100 mg (n=5).
- An outcome was not reported in 4 of 7 cases
- One patient with papilledema was also on fluoxetine, labeled for optic neuritis
- Miosis was reported in a 10 month old after accidental ingestion of 50 mg of a quetiapine and 25 mg of an unspecified antidepressant. Patient was treated with gastric lavage.

Non-Fatal Unlabeled Adverse Events, continued, Seroquel® and Seroquel XR® (quetiapine fumarate)

Gastrointestinal and Hepatic Disorders (n=6)

- Events reported: gastroesophageal reflux disorder (GERD), GI bleed, hepatic enzyme increased, hepatic steatosis, paralytic ileus, and viral gastroenteritis
- Cases: 5 males and 1 female, median age 12 years, range 8 months to 15 years
- 4 cases reported the daily doses of quetiapine: 150 mg, 300 mg, 475 mg, and 800 mg
- GI Bleeding, viral gastroenteritis, and 1 of 2 reports of GERD were related to underlying disorders
- Severity of hepatic enzymes increased could not be assessed since actual transaminase values were not provided
- Case of hepatic steatosis confounded by metabolic syndrome and concomitant use of fluoxetine. Quetiapine labeled for transaminase elevation. Fluoxetine labeled for hepatic failure/necrosis, and hepatitis.
- Cases of GERD and paralytic ileus did not report an outcome

Non-Fatal Unlabeled Adverse Events, continued, Seroquel® and Seroquel XR® (quetiapine fumarate)

Pulmonary/Respiratory/Vascular Disorders (n=4)

- The reported events were pulmonary hypertension, pleural effusion, central sleep apnea (CSA), and pulmonary embolism (PE)
- Cases included 3 females and 1 male, median age of 14 years, range 10 to 16 years
- The total daily dose of quetiapine (n=3) :100 mg daily; “0.5 mg/kg” every morning and “1 mg/kg” every evening; and 200 mg three times daily then overdose with 1200 mg
- The case of PE was complicated by concomitant use of 13 medications, including enoxaparin, an antithrombotic agent
- An outcome was not reported in 3 of 4 cases
- One patient on lithium and quetiapine developed a pleural effusion associated with lithium toxicity and acute kidney injury and made a full recovery

Non-Fatal Unlabeled Adverse Events, continued, Seroquel® and Seroquel XR® (quetiapine fumarate)

Nervous System Disorders (n=3)

- The reported events were loss of consciousness (described as “passed out”)* (n=2), and dementia
- Cases included 3 females, ages 14, 15 and 16 years of age
- None of the cases reported the dose of quetiapine
- None of the cases reported the action taken with quetiapine or an outcome
- None of the cases reported a hospitalization

*labeled for sedation and drowsiness

Non-Fatal Unlabeled Adverse Events, continued, Seroquel® and Seroquel XR® (quetiapine fumarate)

Musculoskeletal Disorders (n=2)

- A female patient, age 15 years, reported excessive sedation, muscle spasm and "could not move" after taking an incorrect dose of quetiapine XR of 300 mg. The event resolved after quetiapine was discontinued.
- A male patient, age 15 years, experienced incontinence, muscular weakness, paresthesia, and visual impairment while receiving quetiapine 25 mg daily and sertraline 50 mg daily for an unspecified indication. The action taken with both medications was not reported, but the events were reported as "improving" at the time of the report.
- Musculoskeletal stiffness and paresthesia are both labeled events under the Adverse Reactions section of the quetiapine labeling

Non-Fatal Unlabeled Adverse Events, continued, Seroquel® and Seroquel XR® (quetiapine fumarate)

Miscellaneous Disorders (n=5)

- The reported events were alopecia, aplastic anemia, hematocolpos, thyroid nodules/ovarian cysts, and ventricular tachycardia
- Cases included 4 females and 1 male, median age of 16 years, range 12 to 16 years
- 16-year-old female with alopecia reported hair loss 7 weeks after starting sertraline at 75 mg and 3 weeks after starting quetiapine at 50 mg. Quetiapine discontinued, sertraline continued, and no other therapy for alopecia was given. No further hair loss was reported after one month.
- 12-year-old patient with ADHD reported ventricular tachycardia when quetiapine XR titrated from 50 mg to 200 mg. The event resolved the same day, and quetiapine was discontinued 9 days later.
- Quetiapine was continued despite reports of aplastic anemia, hematocolpos, thyroid nodules/ovarian cysts in three patients

Summary of Safety Reviews Seroquel® and Seroquel XR® (quetiapine fumarate)

- This concludes the pediatric focused safety review of FAERS reports
- No new safety signals were identified
- FDA recommends continued routine monitoring
- Does the committee concur?

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