Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Adverse Event Review

Date:	December 1, 2011
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Drug Name(s):	Quetiapine fumarate and quetiapine fumarate extended-release
Pediatric Exclusivity Approval Date:	January 23, 2009
Application Type/Number:	NDA #020639, 022047, 022172
Applicant/sponsor:	AstraZeneca
OSE RCM #:	2011-2698

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EXECUTIVE SUMMARY

In accordance with the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Division of Pharmacovigilance (DPV) was asked to summarize post-marketing reports of serious adverse events associated with the use of quetiapine in pediatric patients (0-16 years of age). The main focus of this review is pediatric deaths and pediatric reports of serious unlabeled adverse events with quetiapine fumarate. The consult request highlighted the following serious adverse events; high blood pressure, QT prolongation, metabolic effects, neuromuscular and neuropsychiatric events, neutropenia, leukopenia, and agranulocytosis.

Quetiapine fumarate is an atypical antipsychotic indicated to treat schizophrenia and bipolar mania in pediatric patients.

The Adverse Event Reporting System (AERS) database was searched for all reports of adverse events (serious and non-serious) from December 2, 2009 up to the "data lock" date of July 31, 2011. AERS contained 10,615 reports for quetiapine fumarate. Pediatric reports represented approximately 2.9% of the total (304/10615).

After removing duplicate reports and reconciling null age death values, we identified 176 serious pediatric cases associated with quetiapine, which included 19 deaths and 157 non-fatal post-marketing cases.

Of the 19 cases reporting a fatal outcome, 10 cases reported death by suicide (5), toxicity to various agents (3), and overdose (2). Causes of death in the remaining nine fatal cases varied: death due to an unknown cause (2), cardiomyopathy (1), hepatic failure (1), multi-organ system failure related to congenital heart disease (1), myocardial infarction (1), neuroleptic malignant syndrome (NMS) and QT prolongation (1), shock due to pancreatitis and diabetic ketoacidosis (1), and cardiac arrest in transplacental exposure at six weeks gestation (1).

Across all 157 cases of non-fatal serious outcomes, cases of central nervous system and metabolic adverse events were reported most frequently, and are well-described in the quetiapine label. Additional clinical categories also included reports of cardiac events and hematologic events. Overall, we did not identify any new safety concerns in children 0 – 16 years old treated with quetiapine.

DPV has no recommendations regarding the pediatric population at this time. DPV will continue to monitor adverse events associated with the use of quetiapine.

1 INTRODUCTION

1.1 PRODUCT FORMULATIONS AND INDICATIONS

Seroquel (quetiapine fumarate), an atypical antipsychotic, received FDA approval on September 26, 1997. The mechanism of action of quetiapine is unknown; however, it has been proposed that the efficacy of quetiapine in schizophrenia and its mood stabilizing properties in bipolar depression and mania are mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5HT2) antagonism.

Quetiapine is available in immediate-release and extended-release formulations (XR). Safety and effectiveness of quetiapine XR have not been established in pediatric patients and quetiapine XR is not approved for patients under the age of 18 years. Tables 1 and 2 below provide the recommended dosing schedule for the immediate-release quetiapine, extended-release quetiapine, and their corresponding indications.[1]

Table 1. Dosage and Administration of Immediate-release Quetiapine

Indication	Dosing Instructions*	Recommended Dose / Dose Range	Approval Date**
Schizophrenia-Adults	Day 1: 25 mg twice daily. Increase in increments of 25 mg-50 mg divided two or three times on Days 2 and 3 to range of 300-400 mg by Day 4. Further adjustments can be made in increments of 25–50 mg twice a day, in intervals of not less than 2 days.	150 - 750 mg/day	September 26, 1997
Schizophrenia-Adolescents (13-17 years)	Day 1: 25 mg twice daily. Day 2: Twice daily dosing totaling 100 mg. Day 3: Twice daily dosing totaling 200 mg. Day 4: Twice daily dosing totaling 300 mg. Day 5: Twice daily dosing totaling 400 mg. Further adjustments should be in increments no greater than 100 mg/day within the recommended dose range of 400-800 mg/day. Based on response and tolerability, may be administered three times daily.	400 - 800 mg/day	**December 2, 2009**
Bipolar Mania-Adults Monotherapy or as an adjunct to lithium or divalproex	Day 1: Twice daily dosing totaling 100 mg. Day 2: Twice daily dosing totaling 200 mg. Day 3: Twice daily dosing totaling 300 mg. Day 4: Twice daily dosing totaling 400 mg. Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day.	400 – 800 mg/day	January 12, 2004
Bipolar Mania-Children and Adolescents (10 to 17 years), Monotherapy	Day 1: 25 mg twice daily. Day 2: Twice daily dosing totaling 100mg. Day 3: Twice daily dosing totaling 200 mg. Day 4: Twice daily dosing totaling 300 mg. Day 5: Twice daily dosing totaling 400 mg. Further dosage adjustments should be in increments of no greater than 100 mg/day within the recommended dose range of 400 – 600 mg/day. Based on response and tolerability, may be administered three times daily.	400 – 600 mg/day	**December 2, 2009**
Bipolar Depression-Adults	Administer once daily at bedtime. Day 1: 50mg Day 2: 100 mg Day 3: 200 mg Day 4: 300 mg	300 mg/day	October 20, 2006
Bipolar I Disorder Maintenance Therapy- Adults	Administer twice daily totaling 300-800 mg/day as adjunct to lithium or divalproex. Generally, in maintenance phase, patients continued on the same dose on which they were stabilized.		May 13, 2008

* After initial dosing, adjustments can be made upwards or downwards, if necessary, within the dose range depending upon the clinical response and tolerance of the patient.

** Pediatric approvals are highlighted in **bold.**

Table 2. Dosage and Administration of Extended-release Quetiapine
(SEROQUEL XR has not been evaluated in pediatric patients)

Indication	Dosing Instructions*	Recommended Dose / Dose Range	Approval Date
Schizophrenia	Day 1: 300 mg/day Dose increases can be made at intervals as short as 1 day and in increments of up to 300 mg/day.	400-800 mg/day	May 17, 2007
Schizophrenia Maintenance (Monotherapy)	400 mg/day to 800 mg/day	400 - 800 mg/day	May 17, 2007
Bipolar Mania- Acute monotherapy or as an adjunct to lithium or divalproex	Day 1: 300 mg. Day 2: 600 mg. Day 3: between 400 mg and 800 mg	400 – 800 mg/day	October 8, 2008
Depressive Episodes Associated with Bipolar Disorder	Day 1: 50mg Day 2: 100 mg Day 3: 200 mg Day 4: 300 mg	300 mg/day	October 8, 2008
Bipolar I Disorder - Maintenance Treatment as an adjunct to lithium or divalproex	400 mg/day to 800 mg/day	400 - 800 mg/day	October 8, 2008
Major Depressive Disorder, Adjunctive Therapy with Antidepressants	Day 1 and 2: 50 mg Day 3 and 4: 150 mg	150-300 mg/day	December 2, 2009

* After initial dosing, adjustments can be made upwards or downwards, if necessary, within the dose range depending upon the clinical response and tolerance of the patient.

Quetiapine is available as 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, and 400 mg immediate-release tablets; and 50 mg, 150 mg, 200 mg, 300 mg, and 400 mg extended-release tablets.

1.2 PEDIATRIC FILING HISTORY

This BPCA/PREA review was triggered by the new indications for the treatment of schizophrenia in adolescents 13 to 17 years of age and the treatment of bipolar mania in children and adolescents 10 to 17 years, both approved December 2, 2009.

Pediatric exclusivity was granted January 23, 2009.

The safety and efficacy of quetiapine in the treatment of schizophrenia in adolescents (13 to 17 yrs of age) was established in a single 6-week, international, multicenter, randomized, double-blind, parallel-group, placebo controlled study of quetiapine fumarate immediate release tablets in daily doses of 400 mg and 800 mg compared with placebo (Study 112).

Safety and effectiveness in children < 13 years of age with schizophrenia have not been established.

The safety and efficacy of quetiapine in the treatment of bipolar mania in children and adolescents (10 to 17 yrs of age) was established in a 3-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled study of quetiapine fumarate (Seroquel) immediate-release tablets in daily doses of 400 mg and 600 mg compared with placebo (Study 149).

Safety and effectiveness in children < 10 years of age with bipolar mania have not been established.

Most adverse reactions in pediatric clinical trials were similar to those observed in adults and included somnolence, dizziness, fatigue, increased appetite, nausea, vomiting, dry mouth, tachycardia, and weight increase. However, increases in blood pressure and potentially clinically significant increases in heart rate (> 110 beats per minute [bpm]) occurred in children and adolescents and did not occur in adults.[2, 3]

1.3 PEDIATRIC LABELING

Please see Appendix A for a complete listing of the relevant pediatric labeling.

1.4 PREVIOUS OSE POST-MARKETING SAFETY REVIEWS

There have been a total of five previous post-marketing safety reviews involving quetiapine that specifically addressed safety concerns in pediatric patients. These reviews are detailed below.

- October 4, 2005. A class review of **galactorrhea** with atypical antipsychotic drugs in pediatric patients. The review supported further analysis of hyperprolactinemia and galactorrhea with atypical antipsychotics in order to update risperidone labeling to reflect the increased numbers of reports of hyperprolactinemia and galactorrhea associated with risperidone relative to other atypical antipsychotic drugs.[4]
- October 4, 2005. A class review of **pituitary tumors** with atypical antipsychotic drugs in pediatric patients. The review recommended further investigation, perhaps including reanalysis of the risperidone NDA, in order to update the risperidone label to include increased hyperprolactinemia compared to other atypical antipsychotic agents. [5]
- April 29, 2008. This review focused on **cases of death** in children 16 years old and younger. Quetiapine was associated with 25 death cases. This review concluded that the current safety profile in the labeling would not need revising to include any additional pediatric population specific adverse events.[6]
- May 7, 2009. A review of pediatric postmarketing data for quetiapine in patients aged 0-17 years of age since approval September 26, 1997. The focus of the review was **all pediatric cases of death, metabolic effects (blood triglycerides increased, diabetes mellitus, hyperglycaemia, and weight increased), QT prolongation, and Torsade de pointes**. The safety profile of

the pediatric population is very similar compared to that of the adult population, and the adverse events occurred in much the same manner as well. No new safety signals emerged as part of this review.[7]

- October 14, 2009. As follow-up to a November 18, 2008 Pediatric Advisory Committee (PAC), DPV conducted a pediatric-focused safety review of **extrapyramidal symptoms, hyperprolactinemia, metabolic effects, and precocious puberty** of five atypical antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone). Spontaneous reports of extrapyramidal symptoms (EPS), hyperprolactinemia, and metabolic effects have been reported among the pediatric population in association with the use of aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone; however, often the number of reports are highly variable from drug product to drug product. Precocious puberty was only reported in association with risperidone among the pediatric population. The disproportionality analyses presented in the review showed increased reporting for metabolic effects in association with olanzapine and quetiapine, hypothesis-generating findings, which by themselves may not reflect true agent-specific differences in risk. These findings were consistent with differences identified in a published analysis of clinical trials and in approved labeling for olanzapine. The review concluded that the quetiapine findings should be the subject for further review of data similar to the data reviews that have been used to analyze and label olanzapine.[8]

2 METHODS AND MATERIALS

2.1 AERS SEARCH STRATEGY

The Adverse Event Reporting System (AERS) database was searched with the strategy described in Table 3.

Table 3: AERS Search Strategy*

Date	August 1, 2011
Time period	December 2, 2009** – July 31, 2011
Drug Names	Quetiapine and all associated trade, active ingredient, and verbatim names
Additional criteria	Refer to Appendix B

* See Appendix C for a description of the AERS database.
** This is the approval date of the pediatric schizophrenia and bipolar mania indications

3 RESULTS

3.1 COUNTS OF AERS REPORTS

Table 4: Total number[1] of AERS Reports From December 2, 2009 to July 31, 2011			
	All reports (US)[2]	Serious[3] (US)	Death (US)
Adults (≥ 17 yrs.)	7463 (5969)	5881 (4463)	986 (751)
Pediatrics (0-16 yrs.)	304 (221)	**221 (148)[4]**	37 (33)
Age unknown (Null values)	2848 (2505)	1309 (1013)	149 (118)
Total	10615 (8695)	7411 (5624)	1172 (902)

[1] May include duplicates and have not been assessed for causality

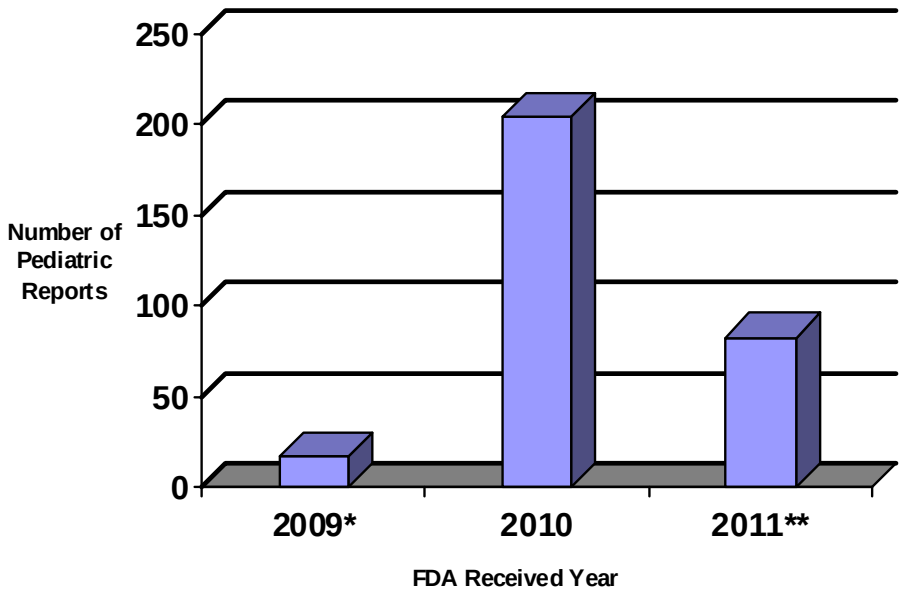
[2] US counts in parentheses

[3] Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.

[4] See Figure 2

Figure 1: Total number of Pediatric Reports (serious and non-serious) for Quetiapine by year of FDA receipt from December 2, 2009 to July 31, 2011 (N=304).

These numbers include data where age (0 - 16 years) is known and may contain duplicate reports.



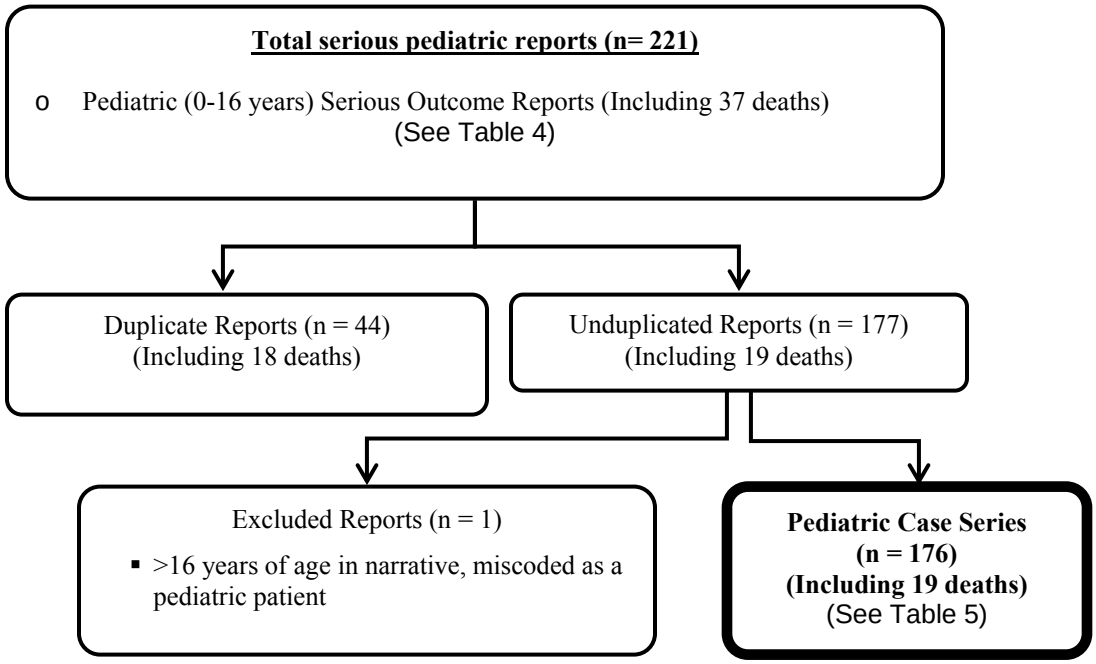
** The 2009 value in Figure 1 represents reports received for quetiapine from December 2, 2009 to December 31, 2009.*

*** The 2011 value in Figure 1 represents reports received for quetiapine from January 1, 2011 to July 31, 2011.*

The reports retrieved in Table 4 for the searches of all adult reports and all pediatric reports from December 2, 2009 to July 31, 2011 did not receive a hands-on analysis; however, these counts are graphically represented by the top 25 preferred terms (PT) reported with quetiapine and by system organ class (SOC) associated with the adverse events (Appendix D).

In addition to reviewing pediatric reports with serious outcomes, we also reviewed all reports with the age unknown reporting an outcome of death to determine if the report concerned a pediatric patient. We reviewed 149 age unknown (null value) death reports and determined that none of the reports involved a pediatric patient. **Figure 2** below summarizes the specific selection of cases to be reviewed in **Section 3.3**.

3.2 FIGURE 2: SELECTION OF SERIOUS PEDIATRIC AERS CASES



3.3 CASE CHARACTERISTICS FROM PEDIATRIC CASE SERIES

Table 5 summarizes the 176 AERS cases from the Pediatric Case Series with quetiapine. Additionally, these reports are graphically represented based on the system organ class

Appendix E contains AERS Case numbers, ISR numbers, and Manufacturer Control Numbers for the Pediatric Case Series.

Table 5: Case characteristics of pediatric case series. December 2, 2009 to July 31, 2011 (N=176)				
Age	0 - <1 month (29)	1 month - <2 years (3)	2-5 years (4)	
	6-11 years (32)	12-16 years (108)		
Gender	Male (89)	Female (83)	Unknown (4)	
Country of occurrence	United States (116)		Foreign (60)	
Event date (n=126)	1997 (1)	1998 (1)	1999 (1)	2000 (5)
	2001 (2)	2002 (2)	2003 (4)	2004 (4)
	2005 (8)	2006 (11)	2007 (3)	2008 (7)
	2009 (24)	2010 (38)	2011 (15)	
Daily dose (n=73)	Mean: 588 mg	Median: 250 mg	Range: 12.5 – 9600 mg	
Duration of therapy (n=58)	Mean: 602 days	Median: 202 days	Range: 1 day – 10 years	
Indications (n=125)	Bipolar Disorder (33) Depression (14) Psychosis/psychotic disorder (11) Sleep disturbances (11) Schizophrenia/Schizoaffective disorder (10) Affective disorder (6) Attention deficit hyperactivity disorder (ADHD) (6) Abnormal behavior (5) Drug exposure during pregnancy (5) Aggression (3) Anxiety (3) Autism (3) Hallucination (2) Mood swings (2) Obsessive-convulsive disorder (2) Adjustment disorder (1) Basal ganglion degeneration (1) Convulsion prophylaxis (1) Impulsive behavior (1) Intermittent explosive disorder (1) Mental retardation (1) Oppositional defiant disorder (1) Pain (1) Psychotherapy (1)			
Primary Outcome[Ψ]	Death (19)	Hospitalized (66)	Disability (4)	
	Life-threatening (5)	Congenital anomaly (5)	Other serious (77)	

[Ψ] Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.

4 DISCUSSION OF SERIOUS PEDIATRIC CASE SERIES

The main focus of this review is pediatric reports of death and pediatric reports of serious unlabeled adverse events with quetiapine fumarate. The consult request highlighted the following serious adverse events; high blood pressure, QT prolongation, metabolic effects, neuromuscular and neuropsychiatric events, neutropenia, leukopenia, and agranulocytosis.

4.1 SUMMARY OF PEDIATRIC DEATHS (N=19)

The AERS database contained 19 pediatric cases received from *December 2, 2009 to July 31, 2011,* with an outcome of death in association with quetiapine use. Death was reported in nine males, eight females, and two patients of unknown gender, ranging in age from 42 days to 16 years, with a median age of 13 years. Sixteen cases were reported from the US and three cases were from foreign report sources.

Overall, 10 cases reported a cause of death related to self-harm or drug misuse including; suicide (5), toxicity to various agents (3), and overdose (2). All five completed suicides were confounded by concomitant medications labeled for suicidality. Three of the five suicide cases reported autopsy results of drug poisoning with quetiapine and/or other medications, while one case reported suicide by coiling a shower hose around the neck and one case reported suicide by hanging. Of these 10 cases, five were literature reports identified in the 2008 or 2009 Annual Report of the American Association of Poison Control Centers National Poison Data System (NPDS).

In addition, three cases reported a cause of death related to cardiac adverse events including; cardiomyopathy that developed subsequent to cessation of quetiapine (1), myocardial infarction (1), and cardiac arrest in transplacental exposure at six weeks gestation (1). The case of cardiac arrest was confounded by an abnormal karyotype analysis.

Causes of death in the remaining six fatal cases varied and included: death due to an unknown cause (2), hepatic failure (1), multi-organ system failure related to congenital heart disease (1), neuroleptic malignant syndrome (NMS) and QT prolongation (1), and shock due to pancreatitis and diabetic ketoacidosis (1). Three of these six cases were confounded by concomitant lithium (labeled for encephalopathic syndrome, which "may be similar to or the same as NMS"[9]) + fluvoxamine (labeled for NMS when co-administered with an antipsychotic) in the case of NMS (1), a history of obesity and a family history of diabetes in the case of shock (1), and congenital aortic valve defect and leaky valve in the case of multi-organ failure (1).

A detailed summary of the fatal pediatric cases can be found in Appendix F.

Suicidality is labeled in the boxed warning, warnings and precautions, adverse reactions, patient counseling information, and medication guide sections of the quetiapine label. Overdose is labeled in the overdose section of the quetiapine label. Cardiomyopathy and pancreatitis are labeled in the adverse reactions. NMS is labeled in warnings and precautions, patient counseling information, and medication guide. Ketoacidosis is labeled in the warnings and precautions. Toxicity to various agents, hepatic failure, multi-organ failure, myocardial infarction, shock, and cardiac arrest are unlabeled events.

4.2 SUMMARY OF NON-FATAL SERIOUS PEDIATRIC ADVERSE EVENTS (N=157)

Of note, the total number of cases discussed in sections 4.2.1 - 4.2.7 amounts to 157 cases, and there is no overlap amongst the case counts.

4.2.1 CENTRAL NERVOUS SYSTEM (CNS) EVENTS (N=44)

We identified 44 cases of serious CNS events in pediatric patients associated with the use of quetiapine. The 44 cases were further categorized into neuropsychiatric events (24), neuromuscular events (14), and general CNS events (6).

Neuropsychiatric Events (n=24)

Twenty-four cases reported neuropsychiatric events, including suicidality (12), aggression (4), self-injurious behavior or ideation (3), hallucination (2), abnormal

behavior (1), drug abuse (1), and obsessive compulsive disorder (OCD) (1). The events were reported in 16 females and 8 males ranging in age from seven to 16 years, with a median of 15 years. The time to onset in seven cases ranged from one day to approximately one year, with a median of 96 days. Twelve cases reported a daily dose which ranged from 12.5 to 9,600 mg, with a median of 600 mg. Seventeen cases were confounded by comorbidities associated with the adverse event [10; self-injury/suicidality reported with comorbid depression or bipolar disorder (5), aggression reported with comorbid ADHD (2), aggression reported with comorbid bipolar disorder (2), hallucination reported with schizophrenia(1)], concomitant medications labeled for suicidality [4; valproic acid (1), sertraline + divalproex (1), lamotrigine (1), and risperidone (1)], noncompliance (2), and a past medical history of OCD in a patient reporting OCD symptoms (1).

Suicidality is labeled in the boxed warning, warnings and precautions, adverse reactions, patient counseling information, and medication guide sections of the label. Self-injurious behavior and ideation are captured under suicidality. Aggression is included in the warnings and precautions, adverse reactions, and med guide sections. Hallucination is included in the adverse reactions. Abnormal behavior, drug abuse, and OCD are unlabeled events.

Neuromuscular Events (n=14)

Fourteen cases reported neuromuscular events, including neuroleptic malignant syndrome (NMS) or NMS-like reaction (4), tardive dyskinesia (TD) (2), chorea and athetosis (1), Sydenham's chorea (1), dystonia (1), muscle spasm + abdominal pain + pyrexia (1), muscle twitching + tic + headache (1), muscle weakness (1), tremor (1), and withdrawal dyskinesia (1). The events were reported in nine males and five females ranging in age from four to 16 years, with a median of 11 years. The time to onset in 11 cases ranged from one day to 150 days, with a median of 27 days. Nine cases reported a daily dose, which ranged from 50 to 400 mg, with a median of 200 mg. Six cases were confounded by concomitant medications labeled for weakness, tremor, and dyskinesia [3; aripiprazole + clonidine labeled for weakness (1), escitalopram + lamotrigine + olanzapine labeled for tremor (1), lamotrigine + lisdexamfetamine labeled for dyskinesia (1)], a possible baseline liver dysfunction secondary to XYY syndrome in combination with the 400 mg daily dose of quetiapine in a 4-year old, as contributing factors in the development of NMS[9] (1), untreated streptococcal infection associated with Sydenham's chorea (1), and dyskinesia occurring three days after abrupt cessation of quetiapine (1).

In the first case reporting TD, a consumer reported that after approximately 6 weeks of quetiapine (formulation and dose unknown) to treat bipolar disorder with some improvement, her 16-year old daughter's dose was increased to quetiapine XR 200 mg once daily. After another 6 weeks at this new dose (approximately 12 weeks of quetiapine therapy total), symptoms started gradually with eye blinking, then "mouth turning", then progressed to neck involvement. TD was diagnosed initially by the psychiatrist that prescribed quetiapine, but no treatment was given. As symptoms worsened, she was seen by a neurologist who also diagnosed TD. Per the reporter, both physicians commented that "they had never seen TD occur so quickly". Seroquel was discontinued and she received diphenhydramine. TD symptoms resolved gradually over the next six months. The patient was not taking any concomitant medications at the time

of the incident. Past medical history included being adopted at three years of age, a questionable traumatic brain injury at birth, history of bupropion use which led to seizure disorder, and a history of aripiprazole use prior to quetiapine (with tapering and a wash-out period between these two medications). She has subsequently taken lithium and divalproex sodium to treat the bipolar disorder, but is presently taking aripiprazole and guanfacine. She presently resides in a residential facility.

In the second case reporting TD, a consumer reported that her 11-year old son developed TD approximately 3 weeks after starting quetiapine at an unknown dose to treat sleep terror. The events were reported as "uncontrollable muscle movements of his limbs and uncontrollable itching of his entire body." The case was confounded by concomitant lisdexamfetamine and lamotrigine which are both labeled for dyskinesia. The outcome of the events was not reported. We have been unable to reach the reporter to obtain follow-up information for this case.

NMS is labeled in the warning and precautions, patient counseling information, and medication guide sections of the label. TD is labeled in the warnings and precautions, adverse reactions, and med guide sections. Itching is labeled as pruritus in the adverse events. Withdrawal is labeled in the warnings and precautions, and the adverse reactions sections. Dyskinesia, chorea, athetosis, dystonia, spasms, pyrexia, abdominal pain, muscle twitching, headache, and tremor are labeled in the adverse reactions section. Tic is an unlabeled event.

General CNS Events (n=6)

Six cases reported various CNS events, including loss of consciousness (3), convulsion (1), sedation (1), and somnolence (1). All three cases of loss of consciousness reported the use of quetiapine in the XR formulation. Five cases were confounded by concomitant medications labeled for amnesia + syncope (1; guanfacine) and syncope (1; lithium), off-label use and lack of dose titration (1), wrong drug administered; the patient thought quetiapine was an analgesic (1), and a medical history of seizure (1).

In the first case of loss of consciousness, a 6-year old male "blacks out whenever he gets angry and does not remember what is going on", in addition to developing warts on his hands and face (coded as skin papilloma) while taking quetiapine XR 200 mg daily and guanfacine 100 mg daily to treat bipolar disorder. The case is confounded by concomitant guanfacine which is labeled for amnesia and syncope.

In another case of loss of consciousness, a 15-year old male who had been in a fight and hurt his eye was subsequently given a single dose of quetiapine XR 150 mg by a fellow student for pain. He became dizzy, blacked out, fell and hit his head. On examination by a physician three hours after ingestion, his speech was slurred and he was sleepy. The outcome was unknown. The case is confounded by off-label use and lack of dose titration.

In the third case of loss of consciousness, a 15-year old male "blacked out" and lost consciousness nine months after starting quetiapine XR 300 mg daily to treat an unknown indication. Concomitant medication included lithium, which is labeled for syncope. Quetiapine was continued and the outcome of the event was unknown.

Loss of consciousness and somnolence are labeled as syncope in the warnings and precautions, and adverse reactions sections of the label. Convulsion is labeled as seizure in the warnings and precautions, overdose section, and med guide sections. Amnesia, sedation, and dysarthria are labeled in the adverse reactions sections. Dizziness is labeled in the adverse reactions, patient counseling information, and med guide sections. Fall is labeled in the warnings and precautions, and patient counseling information sections. Sedation is labeled in the adverse reactions and overdose sections of the label.

4.2.2 METABOLIC EVENTS (N=44)

We identified 44 cases of metabolic adverse events in pediatric patients associated with the use of quetiapine. The 44 cases were further categorized into diabetes mellitus and complications thereof (29), weight abnormalities (12), hypoglycemia (2), and dyslipidemia (1). Among the 44 cases, 41 were reported from the US and three were from foreign report sources. The cases reported quetiapine use in 23 females and 21 males ranging in age from five to 16 years, with a median of 14 years. Twenty-nine cases reported a time to onset of event, which ranged from 24 days to five years, with a median of approximately one year. Thirteen cases reported a daily dose, which ranged from 25 mg to 800 mg, with a median of 200 mg.

Diabetes Mellitus and complications thereof (29)

Twenty-nine cases reported diabetes mellitus and its associated complications as Type 1 diabetes (11), Type 2 diabetes (9), unspecified diabetes (6), diabetic ketoacidosis (2), and borderline diabetes/prediabetic (1). The events were reported in 15 females and 14 males ranging in age from six to 17 years, with a median of 13 years. The time to onset in 22 cases ranged from 24 days to 5.8 years, with a median of approximately one year. Twenty-four cases were reported by attorneys and five cases were reported by physicians. Twenty-five cases were confounded by concomitant medications labeled for diabetes (21), a family history of diabetes (16), a past medical history of obesity (6), and a past medical history of glucose abnormalities prior to taking quetiapine (2).[Σ]

Weight Changes (12)

Eleven cases reported weight gain and one case reported weight loss. These events were reported in seven females and five males ranging in age from nine to 16 years, with a median of 14 years. The time to onset in seven cases ranged from 35 days to 3 years, with a median of 307 days. Seven cases were confounded by concomitant medications labeled for weight gain [6; alprazolam (1), lithium (1), olanzapine + aripiprazole + ziprasidone (1), mirtazapine (1), clozapine (1), risperidone + valproate (1)], a history of being overweight or obese (2), and approximately one year of concomitant dextroamphetamine/amphetamine, which is labeled for weight loss, anorexia, and decreased appetite (1). Overall, ten cases reported the amount of weight gained or lost, which can be found in Table 6 below.

[Σ] Confounding factors are not mutually exclusive to a single case.

Table 6. Weight changes reported in the AERS pediatric case series for quetiapine, organized by age in years[Ω]

Age in Years	Gender	Daily Dose	Amount of Weight Gain or Loss
9	M		
11	F		52 lb weight gain over an unspecified period of time
11	F		13.2 lb weight gain in 7 weeks
12	M		10 lb weight gain per month
12	F	200	43 lb weight *loss* in approximately 1 year
14	M		over 70 lb weight gain over an unspecified period of time
14	F		22 lb weight gain over approximately 1 year
15	F	100	15.4 lb weight gain over 2 months
15	M	800	30 lb weight gain over approximately a 2.5 month period (17 lbs on quetiapine alone, 13 lbs on quetiapine and clozapine)
15	M		over 100 lb weight gain when titrating up to a total of 700mg/day during May 2009
16	F		15 lb weight gain in 1 month after starting quetiapine
16	F		

[Ω] The blank fields in Table 6 represent information omitted from the AERS report by the reporter.

Hypoglycemia (2)

Two non-fatal serious pediatric cases reported hypoglycemia. In the first case, a 13-year old female taking quetiapine for approximately two years to treat bipolar disorder and mood change passed out and fell in the shower. Three months prior to the event, the patient had a fasting blood glucose of 85 (units not reported). Six days prior to the event, her post-prandial blood glucose was 62. Her quetiapine dose at the time of the event was 300 mg daily. She was seen in an urgent care center where she was found to be hypoglycemic. The physician reported that the patient had been "eating a lot of sugar and behaving lethargic for a while, so she might have been hypoglycemic for some time." The patient was not hospitalized and no action was taken with quetiapine. She recovered from the events on an unspecified date. Concomitant medication included trazodone and clonidine.

In the second case, a 16-year old male was hospitalized for hypoglycemia and decreased appetite while taking quetiapine 25 mg daily to treat depression. Concomitant medication included valproate sodium, escitalopram, isotretinoin, and nicotine. The case is confounded by comorbid depression, which may be associated with changes in eating habits; and concomitant escitalopram, which is labeled for decreased appetite.

Dyslipidemia (1)

A 15-year old male taking quetiapine 50 mg daily for more than 2 years to treat autism, depression, and ADHD, experienced elevated serum cholesterol, triglyceride, glucose, AST, and ALT levels. At the time of presentation at an endocrine clinic, blood lipid panel showed elevated fasting cholesterol of 388 mg/dL, triglycerides 1,420 mg/dL, HDL 46 mg/dL and glucose 120mg/dL. Repeat levels of the lipid panel and glucose showed similar elevations two days later. Liver function tests showed elevated AST 47 u/dL and ALT 105 u/dL. Amylase, lipase, thyroid stimulating hormone, fasting insulin, urine micro albumin levels, EKG, echocardiogram, and cardiac examination were normal. Quetiapine was discontinued and replaced with aripiprazole. Four months later, laboratory tests showed a "normalizing" serum cholesterol of 209 mg/dL, triglycerides 261 mg/dL, HDL 44mg/dL, LDL 113 mg/dL, AST 46 u/dL, and ALT 68 u/DL. The patient recovered from the events. The case was confounded by a BMI in the "overweight range".

In 2004, FDA requested that a warning be added to the prescribing information for all atypical antipsychotic medications regarding the increased risk of hyperglycemia and diabetes; therefore, hyperglycemia and diabetes mellitus (including ketoacidosis) are included in the warnings and precautions, adverse reactions, and the patient counseling information sections of the present quetiapine label.

Weight gain is included in the warnings and precautions, adverse reactions, and the patient counseling information sections of the label.

Weight loss, hypoglycemia, elevated AST, and elevated ALT are included in the adverse reactions section of the label.

Dyslipidemia is captured under hyperlipidemia in the warnings and precautions and adverse reactions section of the quetiapine label. Transaminase elevations are labeled in the warnings and precautions, and medication guide.

4.2.3 CARDIAC EVENTS (N=9)

Nine cases reported cardiac events including QT prolongation (3), cardiac arrest (1), AV block (1), cardiac arrest + ventricular fibrillation + QT prolongation (1), chest pain + EKG abnormal (1), increased blood pressure (1), and ventricular extrasystole (1). The events were reported in six males, two females, and one patient of unknown gender. The patients ranged in age from 10 to 16 years, with a median of 13 years. Six cases reported a daily dose, which ranged from 25 to 400mg, with a median of 50 mg. One case reported abatement of ventricular extrasystole after quetiapine was discontinued, and reappearance of the ventricular extrasystole after quetiapine was reintroduced. One case reporting cardiac arrest + ventricular fibrillation + QT prolongation also reported abatement of the QT prolongation after quetiapine was discontinued. All nine cases were confounded by concomitant medications labeled for arrhythmia [amezinium (1)], QT prolongation [atomoxetine (1), aripiprazole + ziprasidone + trazodone (1)], hypertension [escitalopram + bupropion (1)], cardiorespiratory arrest [aripiprazole (1)], and chest pain [dexamphetamine + valproate (1)], congenital heart disease in the case of increased blood pressure (1), overdose with quetiapine, trazodone, and risperidone, which are all labeled

for QT prolongation (1), and in the case of the cardiac arrest, collapse while playing basketball after two years of quetiapine use (1).

Reviewer's Comment: Overall, five cases reported QT prolongation. We discussed one of these cases in Section 4.1, Summary of Pediatric Deaths. We discussed the remaining four cases in Section 4.2.3, Cardiac Events. All five cases were confounded by concomitant medications labeled for QT prolongation (2), comorbid NMS in a fatal case where the cause of death was NMS (1), overdose (1), and in the case of the cardiac arrest, collapse while playing basketball after two years of quetiapine use (1).

QT prolongation is labeled in the warnings and precautions and the adverse reactions sections of the quetiapine label. AV block, chest pain, and electrocardiogram abnormal are labeled in the adverse reactions. Increased blood pressure is labeled in the warnings and precautions. Cardiac arrest and ventricular extrasystole are unlabeled events.

4.2.4 HEMATOLOGIC EVENTS (N=9)

Nine cases reported hematologic events, including leukopenia + neutropenia (3), neutropenia (2), leukopenia (1), methaemoglobinuria + myoglobinuria + liver function test abnormal (1), prothrombin time ratio decreased (1), and thrombocytopenia (1). The events were reported in five males and four females ranging in age from nine to 16 years, with a median of 15 years. The time to onset in eight cases ranged from 3 days to 407 days, with a median of 81 days. Seven cases reported a daily dose, which ranged from 50 mg to 800 mg, with a median of 500 mg. One case reported abatement of leukopenia after the dose of quetiapine was stopped. Eight cases were confounded by concomitant medications labeled for a leukopenia, neutropenia, and/or thrombocytopenia [6; escitalopram + bupropion (1), chloroprothixene (1), oxcarbazepine + divalproex (1), lorazepam (1), valproic acid (1), lamotrigine (1)] and comorbidities [2; Gaucher's disease (1), viral infection (1)].

Leukopenia and neutropenia are labeled in the warnings and precautions, adverse reactions, and patient counseling information sections of the label. Thrombocytopenia is labeled in the adverse reactions. Myoglobinuria is labeled in the warnings and precautions under NMS. Transaminase elevations and abnormal liver tests are labeled in the warnings and precautions, and medication guide. Methaemoglobinuria and prothrombin time ratio decreased are unlabeled events.

4.3 SUMMARY OF REMAINING PEDIATRIC ADVERSE EVENTS (N=51)

DPV was asked to review pediatric deaths and pediatric reports of serious unlabeled adverse events with quetiapine fumarate. The consult request highlighted the following serious adverse events; high blood pressure, QT prolongation, metabolic effects, neuromuscular and neuropsychiatric events, neutropenia, leukopenia, and agranulocytosis, with a comparison of pediatric and adult adverse events. These adverse events are discussed in sections 4.2.1 to 4.2.4. Additionally, we provided the following case counts of all other adverse events reported in the pediatric population (during the period of December 2, 2009 to July 31, 2011) below categorized by system organ class (SOC). Unlabeled adverse events are appended with an asterisk (*).

Adverse event case counts:

- ***Pregnancy, puerperium and perinatal conditions(29):*** drug withdrawal syndrome (10), talipes* (3), respiratory distress (2), congenital hernia* + patent ductus arteriosus* + pulmonary artery stenosis* (1), congenital pulmonary valve atresia* + ventricular septal defect* (1), cyanosis + hypotonia (1), dysmorphism* (1), EPS (1), failure to thrive* + tremor (1), foetal distress syndrome* (1), gastric volvulus* + dysphagia (1), muscle rigidity + dyskinesia + catatonia* (1), neonatal aspiration* (1), pylorus dilatation* (1), premature baby* (1), respiratory disorder + hyperreflexia* + tremor (1), small for dates baby* (1)
- ***Gastrointestinal (7):*** pancreatitis (6), esophageal spasm* (with comorbid cerebral palsy, feeding tube, and history of gastric ulcer) (1)
- ***Injury, poisoning and procedural complications (5):*** accidental drug intake by child (2) , intentional overdose (2), fall (1)
- ***General (4):*** drug ineffective* (2), hypothermia (1), drug withdrawal syndrome (1)
- ***Endocrine (2):*** Cushing's syndrome* (1), hypothyroidism (1)
- ***Eye (2):*** cataract (possibly congenital in one case) (2)
- ***Infections and infestations (2):*** staphylococcal infection + brain abscess* + sinusitis (1), pneumonia (1)

5 CONCLUSIONS

Among the 19 post-marketing pediatric death cases and the 157 non-fatal serious postmarketing cases analyzed in this review, the pediatric safety profile is consistent with the present quetiapine label. Across all cases of non-fatal serious outcomes, cases of central nervous system and metabolic adverse events are reported most frequently, and are well-described in the quetiapine label. Overall, we did not identify any new safety concerns in children 0 – 16 years old treated with quetiapine.

6 RECOMMENDATIONS

DPV has no recommendations regarding quetiapine in the pediatric population at this time. DPV will continue to monitor adverse events associated with the use of quetiapine.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A: DRUG PRODUCT INFORMATION

BOXED WARNING

SUICIDALITY AND ANTIDEPRESSANT DRUGS Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SEROQUEL or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SEROQUEL is not approved for use in patients under ten years of age [*see Warnings and Precautions* (5.2)].

5 WARNINGS AND PRECAUTIONS

5.2 Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 1824) with major depressive disorder (MDD) and other psychiatric disorders.

Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000Patients Treated
Increases Compared to Placebo	
<18	14 additional cases
18-24	5 additional cases
Decreases Compared to Placebo	
25-64	1 fewer case
≥65	6 fewer cases

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that SEROQUEL is approved for use in treating adult bipolar depression.

5.3 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood

pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported.

5.4 Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including quetiapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse reactions is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment.

Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

In some patients, a worsening of more than one of the metabolic parameters of weight, blood glucose and lipids was observed in clinical studies. Changes in these parameters should be managed as clinically appropriate.

***Children and Adolescents*:** In a placebo-controlled SEROQUEL monotherapy study of adolescent patients (13–17 years of age) with schizophrenia (6 weeks duration), the mean change in fasting glucose levels for SEROQUEL (n=138) compared to placebo (n=67) was –0.75 mg/dL versus –1.70 mg/dL. In a placebo-controlled SEROQUEL monotherapy study of children and adolescent patients (10–17 years of age) with bipolar mania (3 weeks duration), the mean change in fasting glucose level for SEROQUEL (n=170) compared to placebo (n=81) was 3.62 mg/dL versus –1.17 mg/dL. No patient in either study with a baseline

normal fasting glucose level (<100 mg/dL) or a baseline borderline fasting glucose level (≥100 mg/dL and <126 mg/dL) had a treatment-emergent blood glucose level of ≥126 mg/dL.

5.5 Hyperlipidemia

Undesirable alterations in lipids have been observed with quetiapine use. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using quetiapine is recommended.

In some patients, a worsening of more than one of the metabolic parameters of weight, blood glucose and lipids was observed in clinical studies. Changes in these parameters should be managed as clinically appropriate.

***Children and Adolescents*:** Table 4 shows the percentage of children and adolescents with changes in total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol from baseline in clinical trials with SEROQUEL.

Table 4: Percentage of Children and Adolescents with Shifts in Total Cholesterol, Triglycerides, LDL-Cholesterol and HDL-Cholesterol from Baseline to Clinically Significant Levels

Laboratory Analyte	Indication	Treatment Arm	N	Patients n (%)
Total Cholesterol ≥200 mg/dL	Schizophrenia[a]	SEROQUEL	107	13 (12%)
		Placebo	56	1 (2%)
	Bipolar Mania[b]	SEROQUEL	159	16 (10%)
		Placebo	66	2 (3%)
Triglycerides ≥150 mg/dL	Schizophrenia[a]	SEROQUEL	103	17 (17%)
		Placebo	51	4 (8%)
	Bipolar Mania[b]	SEROQUEL	149	32 (22%)
		Placebo	60	8 (13%)
LDL-Cholesterol ≥ 130 mg/dL	Schizophrenia[a]	SEROQUEL	112	4 (4%)
		Placebo	60	1 (2%)
	Bipolar Mania[b]	SEROQUEL	169	13 (8%)
		Placebo	74	4 (5%)
HDL-Cholesterol ≤ 40 mg/dL	Schizophrenia[a]	SEROQUEL	104	16 (15%)
		Placebo	54	10 (19%)
	Bipolar Mania[b]	SEROQUEL	154	16 (10%)
		Placebo	61	4 (7%)

a: 13-17 years, 6 weeks duration
b: 10-17 years, 3 weeks duration

5.6 Weight Gain

Increases in weight have been observed in clinical trials. Patients receiving quetiapine should receive regular monitoring of weight [*see Patient Counseling Information* (17)].

In some patients, a worsening of more than one of the metabolic parameters of weight, blood glucose and lipids was observed in clinical studies. Changes in these parameters should be managed as clinically appropriate.

***Children and Adolescents*:** In two clinical trials with SEROQUEL, one in bipolar mania and one in schizophrenia, reported increases in weight are included in the table below.

Table 6: Proportion of Patients with Weight Gain ≥7% of Body Weight (Children and Adolescents)

Vital Sign	Indication	Treatment Arm	N	Patients n (%)
Weight Gain ≥7% of Body Weight	Schizophrenia[a]	SEROQUEL	111	23 (21%)
		Placebo	44	3 (7%)
	Bipolar Mania[b]	SEROQUEL	157	18 (12%)
		Placebo	68	0 (0%)

a: 6 weeks duration
b: 3 weeks duration

The mean change in body weight in the schizophrenia trial was 2.0 kg in the SEROQUEL group and -0.4 kg in the placebo group and in the bipolar mania trial it was 1.7 kg in the SEROQUEL group and 0.4 kg in the placebo group.

In an open-label study that enrolled patients from the above two pediatric trials, 63% of patients (241/380) completed 26 weeks of therapy with SEROQUEL. After 26 weeks of treatment, the mean increase in body weight was 4.4 kg. Forty-five percent of the patients gained ≥ 7% of their body weight, not adjusted for normal growth. In order to adjust for normal growth over 26 weeks an increase of at least 0.5 standard deviation from baseline in BMI was used as a measure of a clinically significant change; 18.3% of patients on SEROQUEL met this criterion after 26 weeks of treatment.

When treating pediatric patients with SEROQUEL for any indication, weight gain should be assessed against that expected for normal growth.

5.7 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs, including quetiapine. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses or may even arise after discontinuation of treatment.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome.

5.9 Increases in Blood Pressure in Children and Adolescents

In placebo-controlled trials in children and adolescents with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of increases at any time in systolic blood pressure (≥20 mmHg) was 15.2% (51/335) for SEROQUEL and 5.5% (9/163) for placebo; the incidence of increases at any time in diastolic blood pressure (≥10 mmHg) was 40.6% (136/335) for SEROQUEL and 24.5% (40/163) for placebo. In the 26week open-label clinical trial, one child with a reported history of hypertension experienced a hypertensive crisis. Blood pressure in children and adolescents should be measured at the beginning of, and periodically during treatment.

5.10 Leukopenia, Neutropenia and Agranulocytosis

In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to atypical antipsychotic agents, including SEROQUEL. Agranulocytosis (including fatal cases) has also been reported.
Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue SEROQUEL at the first sign of a decline in WBC in absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm^3) should discontinue SEROQUEL and have their WBC followed until recovery [*see Adverse Reactions* (6.2)].

5.11 Cataracts

The development of cataracts was observed in association with quetiapine treatment in chronic dog studies [*see Nonclinical Toxicology, Animal Toxicology* (13.2)]. Lens changes have also been observed in adults, children and adolescents during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp

exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6-month intervals during chronic treatment.

5.12 QT Prolongation

In clinical trials quetiapine was not associated with a persistent increase in QT intervals. However, the QT effect was not systematically evaluated in a thorough QT study. In post marketing experience, there were cases reported of QT prolongation in patients who overdosed on quetiapine [*see Overdosage (10.1)*], in patients with concomitant illness, and in patients taking medicines known to cause electrolyte imbalance or increase QT interval [*see Drug Interactions (7)*].

The use of quetiapine should be avoided in combination with other drugs that are known to prolong QTc including Class 1A antiarrythmics (e.g., quinidine, procainamide) or Class III antiarrythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval (e.g., pentamidine, levomethadyl acetate, methadone).
Quetiapine should also be avoided in circumstances that may increase the risk of occurrence of torsade de pointes and/or sudden death including (1) a history of cardiac arrhythmias such as bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

Caution should also be exercised when quetiapine is prescribed in patients with increased risk of QT prolongation (e.g. cardiovascular disease, family history of QT prolongation, the elderly, congestive heart failure and heart hypertrophy).

5.14 Hypothyroidism

***Children and Adolescents*:** In acute placebo-controlled trials in children and adolescent patients with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of shifts to potentially clinically important thyroid function values at any time for SEROQUEL treated patients and placebo-treated patients for elevated TSH was 2.9% (8/280) vs. 0.7% (1/138), respectively and for decreased total thyroxine was 2.8% (8/289) vs. 0% (0/145, respectively). Of the SEROQUEL treated patients with elevated TSH levels, 1 had simultaneous low free T4 level at end of treatment.

5.15 Hyperprolactinemia

***Children and Adolescents*:** In acute placebo-controlled trials in children and adolescent patients with bipolar mania (3-week duration) or schizophrenia (6-week duration), the incidence of shifts in prolactin levels to a clinically significant value (>20 μg/L males; > 26 μg/L females at any time) was 13.4% (18/134) for SEROQUEL compared to 4% (3/75) for placebo in males and 8.7% (9/104) for SEROQUEL compared to 0% (0/39) for placebo in females.
Like other drugs that antagonize dopamine D2 receptors, SEROQUEL elevates prolactin levels in some patients and the elevation may persist during chronic administration. Hyperprolactinemia, regardless of etiology, may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in carcinogenicity studies conducted in mice and rats. Neither clinical

studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive [*see Carcinogenesis, Mutagenesis, Impairment of Fertility* (13.1)].

5.21 Suicide The possibility of a suicide attempt is inherent in bipolar disorder and schizophrenia; close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

In two 8-week clinical studies in patients with bipolar depression (N=1048), the incidence of treatment emergent suicidal ideation or suicide attempt was low and similar to placebo (SEROQUEL 300 mg, 6/350, 1.7%; SEROQUEL 600 mg, 9/348, 2.6%; Placebo, 7/347, 2.0%).

ADVERSE REACTIONS

6.1 Clinical Study Experience

Children and Adolescents: The information below is derived from a clinical trial database for SEROQUEL consisting of over 1000 pediatric patients. This database includes 677 patients exposed to SEROQUEL for the treatment of schizophrenia and 393 patients exposed to SEROQUEL for the treatment of acute bipolar mania.

Incidence of Adverse Reactions in Short-Term, Placebo-Controlled Trials in Children and Adolescents

Adolescents 13 to 17 years of age with Schizophrenia

The following findings were based on a 6-week placebo-controlled trial in which quetiapine was administered in either doses of 400 or 800 mg/day.

Adverse Reactions Associated with Discontinuation of Treatment

The incidence of discontinuation due to adverse reactions for quetiapinetreated and placebo-treated patients was 8.2% and 2.7%, respectively. The adverse event leading to discontinuation in 1% or more of patients on SEROQUEL and at a greater incidence than placebo was somnolence (2.7% and 0% for placebo).

Commonly Observed Adverse Reactions

In therapy for schizophrenia (up to 6 weeks), the most commonly observed adverse reactions associated with the use of quetiapine in adolescents (incidence of 5% or greater and quetiapine incidence at least twice that for placebo) were somnolence (34%), dizziness (12%), dry mouth (7%), tachycardia (7%).

Table 12 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during therapy (up to 6 weeks) of schizophrenia in 5% or more of patients treated with SEROQUEL (doses of 400 or 800 mg/day) where the incidence in patients treated with SEROQUEL was at least twice the incidence in placebo-treated patients.

Adverse events that were potentially dose-related with higher frequency in the 800 mg group compared to the 400 mg group included dizziness (8.2% vs. 14.9%), dry mouth (4.1% vs. 9.5%), and tachycardia (5.5% vs. 8.1%).

Table 12. Treatment-Emergent Adverse Reaction Incidence in a 6-Week Placebo-Controlled Clinical Trial for the Treatment of Schizophrenia in Adolescent Patients

Body System/Preferred Term	SEROQUEL (n=147)	PLACEBO (n=75)
Central Nervous System Disorders		

Somnolence[1]	34%	11%
Digestive		
Dry Mouth	7%	1%
Cardiovascular Disorders		
Tachycardia	7%	0%
Nervous system Disorder		
Dizziness	12%	5%

[1]Somnolence combines adverse event terms somnolence and sedation

Children and Adolescents 10 to 17 years of age with Bipolar Mania

The following findings were based on a 3-week placebo-controlled trial in which quetiapine was administered in either doses of 400 or 600 mg/day.

Adverse Reactions Associated with Discontinuation of Treatment

The incidence of discontinuation due to adverse reactions for quetiapine-treated and placebo-treated patients was 11.4% and 4.4%, respectively. The adverse events leading to discontinuation in 1% or more of patients on SEROQUEL and at a greater incidence than placebo were somnolence (4.1% vs. 1.1%), fatigue (2.1% vs. 0), irritability (1.6% vs. 0) and syncope (1% vs. 0).

Commonly Observed Adverse Reactions

In bipolar mania therapy (up to 3 weeks) the most commonly observed adverse reactions associated with the use of quetiapine in children and adolescents (incidence of 5% or greater and quetiapine incidence at least twice that for placebo) were somnolence (53%), dizziness (18%), fatigue (11%), increased appetite (9%), nausea (8%), vomiting (8%), tachycardia (7%), dry mouth (7%), and weight increased (6%)**.**

Table 13 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during therapy (up to 3 weeks) of bipolar mania in 5% or more of patients treated with SEROQUEL (doses of 400 or 600 mg/day) where the incidence in patients treated with SEROQUEL was at least twice the incidence in placebo-treated patients.

Adverse events that were potentially dose-related with higher frequency in the 600 mg group compared to the 400 mg group included somnolence (49% vs. 57%), nausea (6.3% vs. 10.2%) and tachycardia (5.3% vs. 8.2%).

Table 13 Treatment-Emergent Adverse Reaction Incidence in a 3-Week Placebo-Controlled Clinical Trial for the Treatment of Bipolar Mania in Children and Adolescent Patients

Body System/Preferred Term	**SEROQUEL (n=193)**	**PLACEBO (n=90)**
Nervous System Disorders		
Somnolence[1]	53%	14%
Dizziness	18%	2%
Fatigue	11%	4%

Metabolism and Nutrition Disorders		
Increased Appetite	9%	1%
Weight Increased	6%	0%
Gastrointestinal Disorders		
Nausea	8%	4%
Vomiting	8%	3%
Dry Mouth	7%	0%
Cardiac Disorders		
Tachycardia	7%	0%

[1]Somnolence combines adverse event terms somnolence and sedation

Adverse Reactions in Schizophrenia and Bipolar Mania Clinical Trials

Commonly Observed Adverse Reactions

In acute therapy for schizophrenia and bipolar mania (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania) the most commonly observed adverse reactions associated with the use of quetiapine in children and adolescents (incidence of 5% or greater and quetiapine incidence at least twice that for placebo) were somnolence (47%), dizziness (15%), fatigue (9%), increased appetite (8%), dry mouth (7%), tachycardia (7%), and weight increased (5%).

Table 14 enumerates the pooled incidence of adverse reactions that occurred during acute therapy of children and adolescents (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania). The table includes only those reactions that occurred in 1% or more of patients treated with quetiapine (doses of 400, 600, or 800 mg/day) and for which the incidence in patients treated with quetiapine was greater than the incidence in patients treated with placebo.

Table 14. Adverse Reactions (incidence ≥ 1% and greater than placebo) in Short-Term, Placebo-Controlled Trials of Children and Adolescents (10 to 17 years of age) with Bipolar Mania or Schizophrenia[1]

Body System/ Preferred Term	**SEROQUEL (n=340)**	**PLACEBO (n=165)**
Central/Nervous System Disorder		
Somnolence[2]	47%	15%
Dizziness	15%	4%
Fatigue	9%	4%
Irritability	4%	1%
Tremor	3%	2%
Akathisia	2%	1%
Syncope	2%	0%

Lethargy	1%	0%
Metabolism and Nutrition Disorders		
Increased Appetite	8%	2%
Weight Increased	5%	1%
Digestive		
Dry Mouth	7%	1%
Cardiovascular Disorders		
Tachycardia	8%	0%
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	3%	1%
Back Pain	2%	1%
Musculoskeletal Stiffness	2%	1%
Respiratory, Thoracic and Mediastinal Disorder		
Nasal Congestion	3%	2%
Gastrointestinal Disorder		
Vomiting	7%	6%
Stomach Discomfort	2%	1%
Skin and Subcutaneous Tissue Disorders		
Acne	2%	1%
General Disorders and Administration Site Conditions		
Pyrexia	2%	1%
Asthenia	2%	1%
Psychiatric Disorders		
Aggression	2%	1%
Restlessness	1%	0%
Eye Disorders		
Vision Blurred	2%	1%

Infections and Infestations		
Tooth Abscess	1%	0%

[1] Threshold criteria were applied before rounding to the nearest integer
[2] Somnolence combines adverse event terms somnolence and sedation

Extrapyramidal Symptoms:

In a short-term placebo-controlled monotherapy trial in adolescent patients with schizophrenia (6-week duration), the aggregated incidence of extrapyramidal symptoms was 12.9% for SEROQUEL and 5.3% for placebo, though the incidence of the individual adverse events (akathisia, tremor, extrapyramidal disorder, hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity, dyskinesia) did not exceed 4.1% in any treatment group. In a short-term placebo-controlled monotherapy trial in children and adolescent patients with bipolar mania (3-week duration), the aggregated incidence of extrapyramidal symptoms was 3.6% for SEROQUEL and 1.1% for placebo.

Table 15 below presents a listing of patients with AEs potentially associated with EPS in the short-term placebo-controlled monotherapy trial in adolescent patients with schizophrenia (6-week duration).

Table 15 Adverse experiences potentially associated with EPS in the short-term placebo-controlled monotherapy trial in adolescent patients with schizophrenia (6week duration)

Table 15 Adverse experiences potentially associated with EPS in the short-term placebo-controlled monotherapy trial in adolescent patients with schizophrenia (6-week duration)

Preferred Term	Placebo (N=75)		SEROQUEL 400 mg/day (N=73)		SEROQUEL 800 mg/day (N=74)		All SEROQUEL (N=147)	
	n	%	n	%	n	%	n	%
Dystonic event[a]	0	0.0	2	2.7	0	0.0	2	1.4
Parkinsonism[b]	2	2.7	4	5.5	4	5.4	8	5.4
Akathisia[c]	3	4.0	3	4.1	4	5.4	7	4.8
Dyskinetic event[d]	0	0.0	2	2.7	0	0.0	2	1.4
Other Extrapyramidal Event[e]	0	0.0	2	2.7	2	2.7	4	2.7

a: Patients with the following terms were counted in this category: nuchal rigidity, hypertonia, dystonia, muscle rigidity
b: Patients with the following terms were counted in this category: cogwheel rigidity, tremor
c: Patients with the following terms were counted in this category: akathisia
d: Patients with the following terms were counted in this category: tardive dyskinesia, dyskinesia, choreoathetosis
e: Patients with the following terms were counted in this category: restlessness; extrapyramidal disorder

Table 16 below presents a listing of patients with Adverse Experiences potentially associated with EPS in a short-term placebo-controlled monotherapy trial in children and adolescent patients with bipolar mania (3-week duration).

Table 16: Adverse experiences potentially associated with EPS in a short-term placebo-controlled monotherapy trial in children and adolescent patients with bipolar mania (3-week duration)

Table 16: Adverse experiences potentially associated with EPS in a short-term placebo-controlled monotherapy trial in children and adolescent patients with bipolar mania (3-week duration)

Preferred Term*	Placebo (N=90)		SEROQUEL 400 mg/day (N=95)		SEROQUEL 600 mg/day (N=98)		All SEROQUEL (N=193)	
	n	%	n	%	n	%	n	%
Parkinsonism[a]	1	1.1	2	2.1	1	1.0	3	1.6
Akathisia[b]	0	0.0	1	1.0	1	1.0	2	1.0
Other Extrapyramidal Event[c]	0	0.0	1	1.1	1	1.0	2	1.0

*: There were no adverse experiences with the preferred term of dystonic or dyskinetic events.
a: Patients with the following terms were counted in this category: cogwheel rigidity, tremor
b: Patients with the following terms were counted in this category: akathisia
c: Patients with the following terms were counted in this category: restlessness; extrapyramidal disorder

Adverse Reactions in Long-Term Open-Label Trial

The adverse reactions reported in a 26-week, open-label trial with SEROQUEL in 5% or greater of the children and adolescent patients with schizophrenia or bipolar mania were somnolence (30%), headache (19%), vomiting (11%), increased weight (13%), insomnia (8%), nausea (10%), fatigue (8%), dizziness (9%), increased appetite (7%), upper respiratory tract infection (7%), agitation (5%), tachycardia (5%), and irritability (5%).

Other Adverse Reactions Observed During the Pre-Marketing Evaluation of SEROQUEL

Following is a list of COSTART terms that reflect treatment-emergent adverse reactions as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with SEROQUEL at multiple doses ≥ 75 mg/day during any phase of a trial within the premarketing database of approximately 2200 patients treated for schizophrenia. All reported reactions are included except those already listed in the tables or elsewhere in labeling, those reactions for which a drug cause was remote, and those reaction terms which were so general as to be uninformative. It is important to emphasize that, although the reactions reported occurred during treatment with SEROQUEL, they were not necessarily caused by it.

Reactions are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients.

Nervous System: ***Infrequent:*** abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased*, urinary retention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonic reaction, hemiplegia; ***Rare:*** aphasia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased*, neuralgia, stuttering, subdural hematoma.

Body as a Whole: ***Frequent:*** flu syndrome; ***Infrequent:*** neck pain, pelvic pain*, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; ***Rare:*** abdomen enlarged.

Digestive System: ***Frequent:*** anorexia; ***Infrequent:*** increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids,

stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; ***Rare:*** glossitis, hematemesis, intestinal obstruction, melena, pancreatitis.

Cardiovascular System: ***Infrequent:*** vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; ***Rare:*** angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration.

Respiratory System: ***Frequent:*** cough increased, dyspnea; ***Infrequent:*** pneumonia, epistaxis, asthma; ***Rare:*** hiccup, hyperventilation.

Metabolic and Nutritional System: ***Infrequent:*** weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; ***Rare:*** glycosuria, gout, hand edema, hypokalemia, water intoxication.

Skin and Appendages System: ***Infrequent:*** pruritus, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; ***Rare:*** exfoliative dermatitis, psoriasis, skin discoloration.

Urogenital System: ***Infrequent:*** dysmenorrhea*, vaginitis*, urinary incontinence, metrorrhagia*, impotence*, dysuria, vaginal moniliasis*, abnormal ejaculation*, cystitis, urinary frequency, amenorrhea*, female lactation*, leukorrhea*, vaginal hemorrhage*, vulvovaginitis* orchitis*; ***Rare:*** gynecomastia*, nocturia, polyuria, acute kidney failure.

Special Senses: ***Infrequent:*** conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; ***Rare:*** abnormality of accommodation, deafness, glaucoma.

Musculoskeletal System: ***Infrequent:*** pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain.

Hemic and Lymphatic System: ***Infrequent:*** leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia; lymphadenopathy, cyanosis; ***Rare:*** hemolysis, thrombocytopenia.

Endocrine System: ***Infrequent:*** hypothyroidism, diabetes mellitus; ***Rare:*** hyperthyroidism. *adjusted for gender

6.2 Vital Signs and Laboratory Values

Hyperglycemia, hyperlipidemia, weight gain, orthostatic hypotension and changes in thyroid hormone levels have been reported with quetiapine. Increases in blood pressure have also been reported with quetiapine in children and adolescents [*see Warnings and Precautions* (5.4, 5.5, 5.6, 5.8, 5.9 and 5.14)].

Children and Adolescents: In the acute (6 week) schizophrenia trial in adolescents, potentially clinically significant increases in heart rate (> 110 bpm) occurred in 5.2% (3/73) of patients receiving SEROQUEL 400 mg and 8.5% (5/74) of patients receiving SEROQUEL 800 mg compared to 0% (0/75) of patients receiving placebo. Mean increases in heart rate were
3.8 bpm and 11.2 bpm for SEROQUEL 400 mg and 800 mg groups, respectively, compared to a decrease of 3.3 bpm in the placebo group [*see Warnings and Precautions* (5.8)].

In the acute (3 week) bipolar mania trial in children and adolescents, potentially clinically significant increases in heart rate (> 110 bpm) occurred in 1.1% (1/95) of patients receiving SEROQUEL 400 mg and 2.4% (2/98) of patients receiving SEROQUEL 600 mg compared to 0% (0/98) of patients receiving placebo. Mean increases in heart rate were
12.8 bpm and 13.4 bpm for SEROQUEL 400 mg and 600 mg groups, respectively, compared to a decrease of 1.7 bpm in the placebo group [*see Warnings and Precautions* (5.8)].

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use In general, the adverse reactions observed in children and adolescents during the clinical trials were similar to those in the adult population with few exceptions. Increases in systolic and diastolic blood pressure occurred in children and adolescents and did not occur in adults. Orthostatic hypotension occurred more frequently in adults (4-7%) compared to children and adolescents (< 1%).

Schizophrenia

The efficacy and safety of SEROQUEL in the treatment of schizophrenia in adolescents aged 13 to 17 years were demonstrated in one 6-week, double-blind, placebo-controlled trial [see *Indications and Usage* (1.1), *Dosage and Administration* (2.1), *Adverse Reactions* (6.1), and *Clinical Studies* (14.1)].

Safety and effectiveness of SEROQUEL in pediatric patients less than 13 years of age with schizophrenia have not been established.

Maintenance

The safety and effectiveness of SEROQUEL in the maintenance treatment of bipolar disorder has not been established in pediatric patients less than 18 years of age. The safety and effectiveness of SEROQUEL in the maintenance treatment of schizophrenia has not been established in any patient population, including pediatric patients.

Bipolar Mania

The efficacy and safety of SEROQUEL in the treatment of mania in children and adolescents ages 10 to 17 years with Bipolar I disorder was demonstrated in a 3-week, double-blind, placebo controlled, multicenter trial [*see Indications and Usage* (1.2), *Dosage and Administration* (2.2), *Adverse Reactions* (6.1), and *Clinical Studies* (14.2)].
Safety and effectiveness of SEROQUEL in pediatric patients less than 10 years of age with bipolar mania have not been established.

Bipolar Depression

Safety and effectiveness of SEROQUEL in pediatric patients less than 18 years of age with bipolar depression have not been established.

Some differences in the pharmacokinetics of quetiapine were noted between children/adolescents (10 to 17 years of age) and adults. When adjusted for weight, the AUC and Cmax of quetiapine were 41% and 39% lower, respectively, in children and adolescents compared to adults. The pharmacokinetics of the active metabolite, norquetiapine, were similar between children/adolescents and adults after adjusting for weight [*see Clinical Pharmacology* (12.3)].

12.3 Pharmacokinetics

Children and Adolescents

At steady-state the pharmacokinetics of the parent compound, in children and adolescents (10-17 years of age), were similar to adults. However, when adjusted for dose and weight, AUC and Cmax of the parent

compound were 41% and 39% lower, respectively, in children and adolescents than in adults. For the active metabolite, norquetiapine, AUC and Cmax were 45% and 31% higher, respectively, in children and adolescents than in adults. When adjusted for dose and weight, the pharmacokinetics of the metabolite, norquetiapine, was similar between children and adolescents and adults [*see Use in Specific Populations* (8.4)].

14 CLINICAL STUDIES

14.2 Bipolar Disorder
Manic Episodes

Children and Adolescents (ages 10-17)

The efficacy of SEROQUEL in the acute treatment of manic episodes associated with bipolar I disorder in children and adolescents (10 to 17 years of age) was demonstrated in a 3-week, double-blind, placebo-controlled, multicenter trial. Patients who met DSM-IV diagnostic criteria for a manic episode were randomized into one of three treatment groups: SEROQUEL 400 mg/day (n = 95), SEROQUEL 600 mg/day (n = 98), or placebo (n = 91). Study medication was initiated at 50 mg/day and on day 2 increased to 100 mg/day (divided doses given two or three times daily). Subsequently, the dose was titrated to a target dose of 400 mg/day or 600 mg/day using increments of 100 mg/day, given in divided doses two or three times daily. The primary efficacy variable was the mean change from baseline in total YMRS score.

SEROQUEL 400 mg/day and 600 mg/day were superior to placebo in the reduction of YMRS total score.

17 PATIENT COUNSELING INFORMATION

Increased Blood Pressure in Children and Adolescents

Blood pressure should be measured at the beginning of, and periodically during, treatment [s*ee Warnings and Precautions* (5.9)].

MEDICATION GUIDE
SEROQUEL (SER-oh-kwell)
(quetiapine fumarate)
Tablets

Read this Medication Guide before you start taking SEROQUEL and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about SEROQUEL?

Serious side effects may happen when you take SEROQUEL, including

• Risk of death in the elderly with dementia: Medicines like SEROQUEL can raise the risk of death in elderly people who have lost touch with reality due to confusion and memory loss (dementia).

SEROQUEL is not approved for treating psychosis in the elderly with dementia.

• Risk of suicidal thoughts or actions: Antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions:

1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.

• Not all antidepressant medicines prescribed for children are FDA approved for use in children.
Talk to your child's healthcare provider for more information.

What is SEROQUEL?

- SEROQUEL is used to treat manic episodes associated with bipolar I disorder in children ages 10 to 17 years. SEROQUEL has not been studied in patients younger than 10 years of age.

What are possible side effects of SEROQUEL?

Serious side effects have been reported with SEROQUEL including:

- **Increases in blood pressure:** reported in children and teenagers. Your healthcare provider should check blood pressure in children and adolescents before starting SEROQUEL and during therapy.

Common possible side effects with SEROQUEL include:

Children and Adolescents:

- drowsiness
- fatigue
- nausea
- dry mouth
- weight gain
- dizziness
- increased appetite
- vomiting
- rapid heart beat

8.2 APPENDIX B: STANDARD SEARCHES

A. Adults (17 yrs and above)
   1. All outcomes from December 2, 2009 (no set criteria)
   2. Serious outcomes from December 2, 2009
   3. Death as an outcome from December 2, 2009

B. Ages 0-16 yrs ONLY
   1. Same as above 1-3
   2. Retrieve case reports for hands-on review

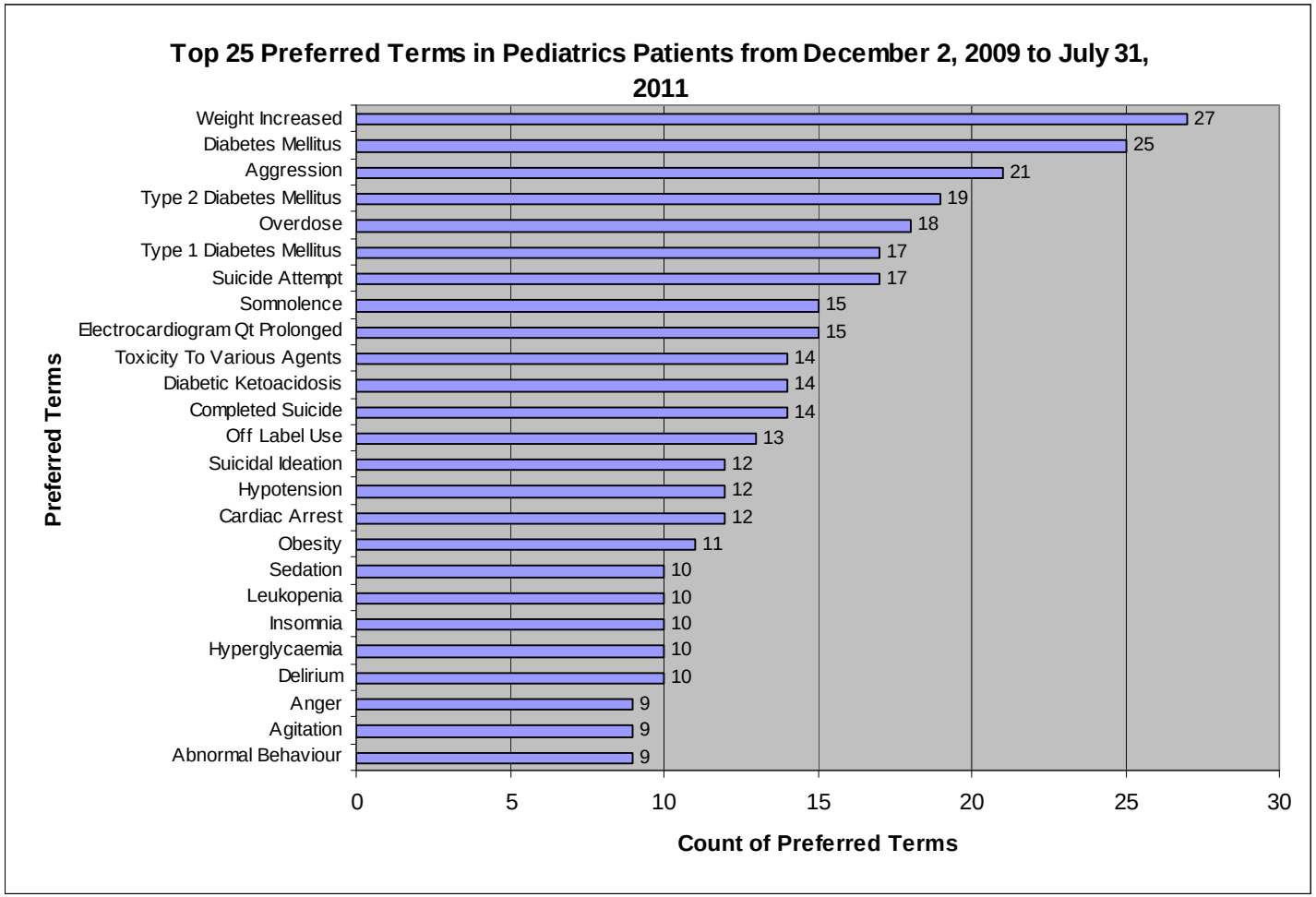
8.3 APPENDIX C: AERS DATABASE DESCRIPTION

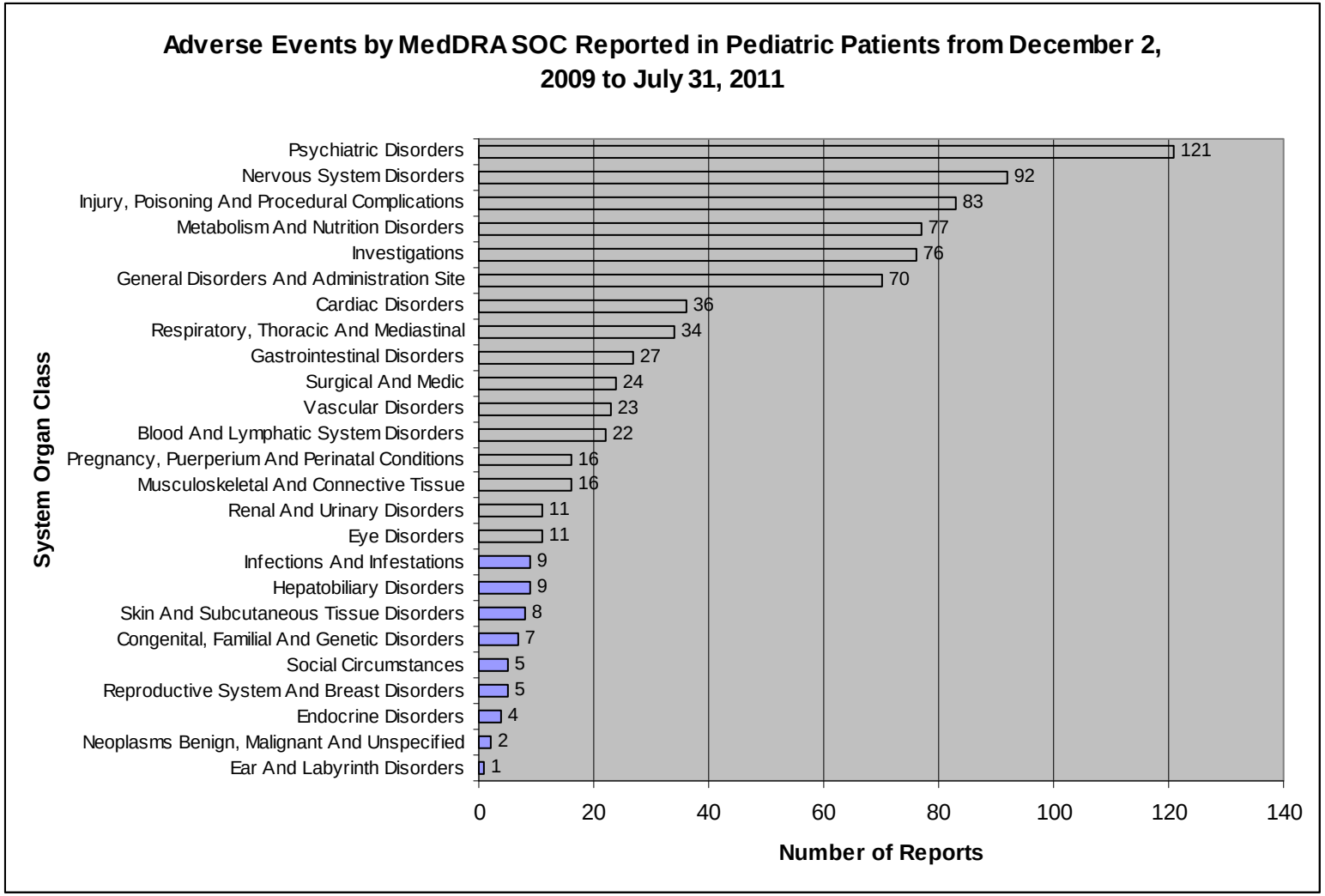
The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonization. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

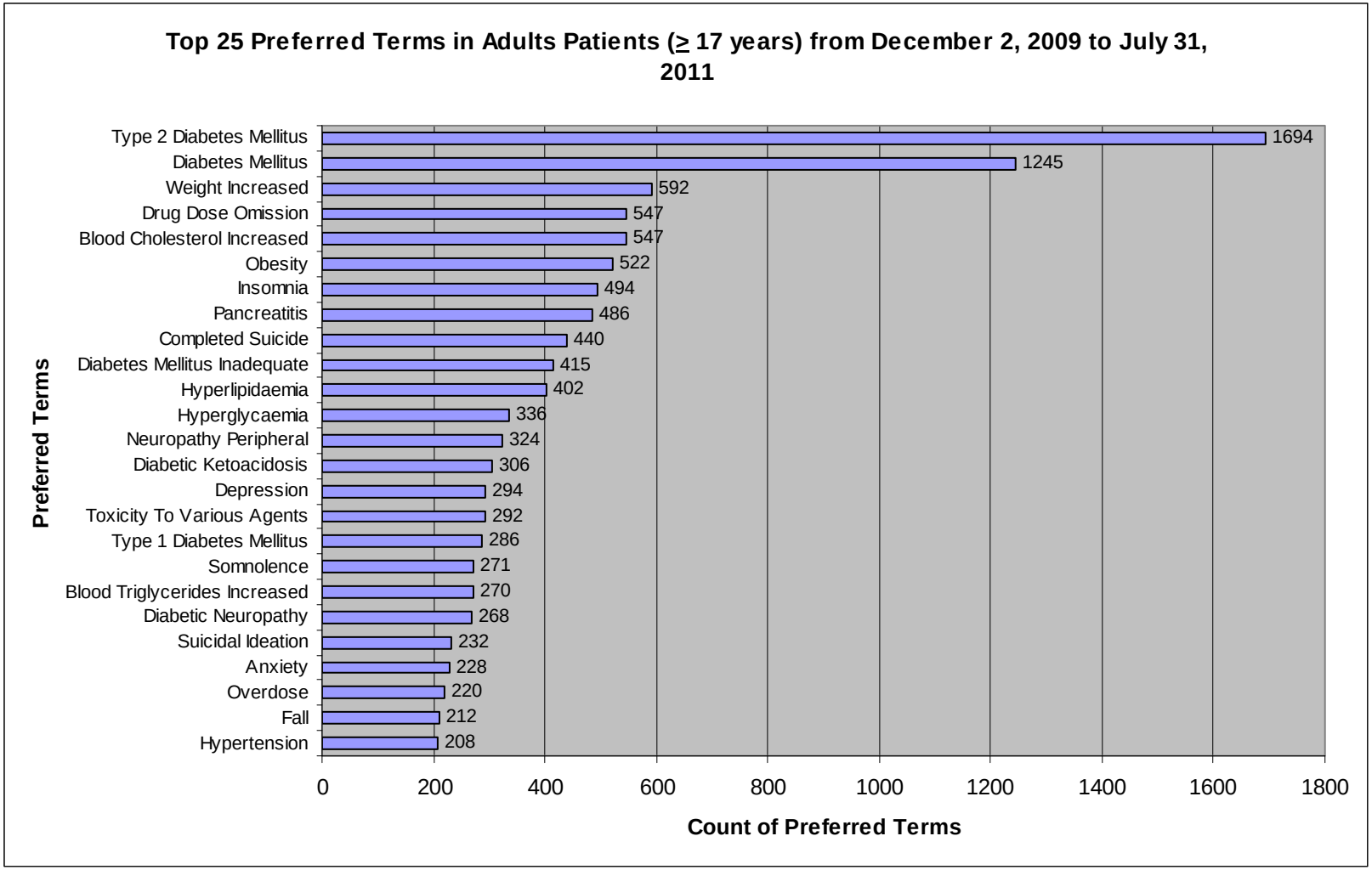
AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

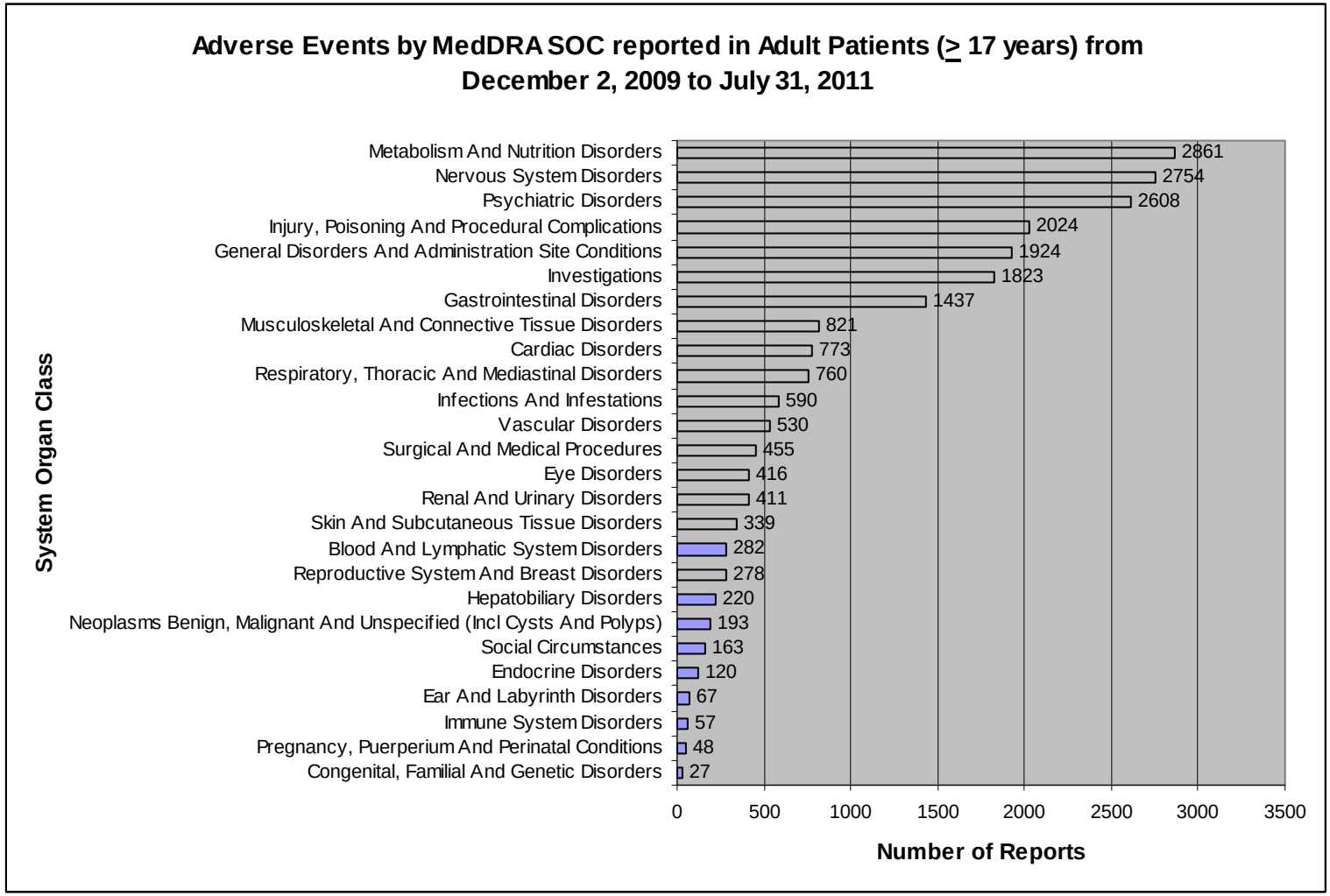
8.4 APPENDIX D: PEDIATRIC VS. ADULT ADVERSE EVENT GRAPHICAL REPRESENTATIONS

The following four charts may contain duplicate reports, in addition to events reporting both serious and non-serious outcomes.








Adverse Events by MedDRA SOC reported in Adult Patients (≥ 17 years) from December 2, 2009 to July 31, 2011
System Organ Class
Metabolism And Nutrition Disorders 2861
Nervous System Disorders 2754
Psychiatric Disorders 2608
Injury, Poisoning And Procedural Complications 2024
General Disorders And Administration Site Conditions 1924
Investigations 1823
Gastrointestinal Disorders 1437
Musculoskeletal And Connective Tissue Disorders 821
Cardiac Disorders 773
Respiratory, Thoracic And Mediastinal Disorders 760
Infections And Infestations 590
Vascular Disorders 530
Surgical And Medical Procedures 455
Eye Disorders 416
Renal And Urinary Disorders 411
Skin And Subcutaneous Tissue Disorders 339
Blood And Lymphatic System Disorders 282
Reproductive System And Breast Disorders 278
Hepatobiliary Disorders 220
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps) 193
Social Circumstances 163
Endocrine Disorders 120
Ear And Labyrinth Disorders 67
Immune System Disorders 57
Pregnancy, Puerperium And Perinatal Conditions 48
Congenital, Familial And Genetic Disorders 27
0 500 1000 1500 2000 2500 3000 3500
Number of Reports

8.5 APPENDIX E: AERS CASE NUMBERS/ISR NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR PEDIATRIC CASE SERIES

Case Number	ISR Number	Manufacturer Control Number		Case Number	ISR Number	Manufacturer Control Number
7165199	6480499	AU-ASTRAZENECA-2009SE22281	[redacted]	7472230	6839032	US-ASTRAZENECA-2010SE32085
7209772	6486619	US-ASTRAZENECA-2009SE30700	[redacted]	7476060	6843540	DE-ASTRAZENECA-2010SE32501
7215462	6494653	US-BRISTOL-MYERS SQUIBB COMPANY-14541288	[redacted]	7491434	6862074	CH-ASTRAZENECA-2010SE32513
7218614	6498607	US-ASTRAZENECA-2009SE31118	[redacted]	7503227	6877001	US-ASTRAZENECA-2010SE34078
7222800	6505220	US-ASTRAZENECA-2009SE31136	[redacted]	7285405	6899879	CO-ASTRAZENECA-2010SE06148
7223601	6505528	CTU 402038	[redacted]	7541410	6924574	CH-ASTRAZENECA-2010SE38038
7223312	6506051	AU-JNJFOC-20091203109	[redacted]	7547205	6932514	US-ASTRAZENECA-2010SE37508
7232240	6518158	CTU 402589	[redacted]	7548982	6934521	CH-ABBOTT-10P-151-0663922-00
7232640	6518257	CTU 402494	[redacted]	7549971	6936013	BE-ASTRAZENECA-2010SE38542
7230896	6518483	TR-JNJFOC-20091205265	[redacted]	7539580	6955346	JP-ASTRAZENECA-2010SE29519
7225949	6521591	CA-ASTRAZENECA-2009SE32470	[redacted]	7527076	6963940	1000015135
7241803	6532941	US-ASTRAZENECA-2010SE00857	[redacted]	7575882	6969939	US-ASTRAZENECA-2007UW18749
7242339	6533709	US-ASTRAZENECA-2010SE00830	[redacted]	7577515	6972516	AU-ASTRAZENECA-2009SE22690
7248807	6541742	GB-MYLANLABS-MK-6006607	[redacted]	7580528	6976683	US-ASTRAZENECA-2010SE41551
7248936	6541911	AU-ASTRAZENECA-2009SE31128	[redacted]	7582396	6978872	US-ASTRAZENECA-2010SE41560
7260410	6557339	US-JNJFOC-20100108252	[redacted]	7591407	6993384	US-ASTRAZENECA-2010SE23549
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7432484	6790670	US-ASTRAZENECA-2010SE27817	[redacted]	7595942	6999926	US-ASTRAZENECA-2010SE14099
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7596750	7001029	US-ASTRAZENECA-2009SE11127		7935450	7465589	AU-ASTRAZENECA-2011SE25133
6418208	7001755	US-ASTRAZENECA-2007UW04263		7928790	7465761	DE-ASTRAZENECA-2011SE24389
6769308	7001772	US-ASTRAZENECA-2007UW13589		7936126	7466466	CH-ASTRAZENECA-2011SE24929
7597329	7001844	US-ASTRAZENECA-2009SE33260		7943373	7477571	IT-JNJFOC-20110502045
7131914	7002086	US-ASTRAZENECA-2009UW09069		7054165	7490088	US-ASTRAZENECA-2009UW20142
6420527	7002094	US-ASTRAZENECA-2007UW09619		7952298	7491755	BR-ASTRAZENECA-2011SE28033
7597567	7002262	US-ASTRAZENECA-2010SE15496		7958060	7500241	GB-ASTRAZENECA-2011SE30872
6279003	7003033	US-ASTRAZENECA-2005UW13236		7964640	7509532	US-ASTRAZENECA-2011SE31225
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7618807	7011079	CTU 430337		7902259	7515116	AU-ASTRAZENECA-2011SE21286
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7605257	7012284	GB-ASTRAZENECA-2010SE39662		7976058	7526454	CN-ASTRAZENECA-2011SE32846
7458001	7024577	GB-ASTRAZENECA-2010SE30920		7979815	7531562	US-ASTRAZENECA-2011SE33251
7618624	7030397	US-ASTRAZENECA-2010SE36567		7684311	7541792	MY-JNJFOC-20080105967
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7684546	7093555	US-000172		8007692	7570233	AU-ASTRAZENECA-2011SE33288
7668854	7103049	CH-ASTRAZENECA-2010SE52908		8019173	7587333	GB-ASTRAZENECA-2011SE37978
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7678235	7116054	US-ASTRAZENECA-2010SE54422		8054259	7635452	US-FDA-7635452
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7279391	7239436	US-ASTRAZENECA-2010SE05543				
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7707488	7404843	US-JNJFOC-20101204399				

8.6 APPENDIX F: DETAILED SUMMARY OF FATAL PEDIATRIC CASES (N=19)

Suicide

ISR# 6532941; US, 2010. A 16-year old female died following intentional suicide; drug poisoning with oral quetiapine, acetaminophen, dextromethorphan, and lamotrigine. On autopsy, the serum drug level of quetiapine was 9000ng/ml.

ISR# 6802895; US, 2010. A 7-year old male died from suicide while being treated with quetiapine for an unknown indication and duration. The patient locked himself in the bathroom of his home, and coiled a shower hose around his neck. Concomitant medications included fluoxetine and olanzapine.

ISR# 6877001; US, 2010. A 15-year old female receiving quetiapine 200 mg daily for an unknown indication and duration committed suicide by hanging. Concomitant medication included fluoxetine.

ISR# 7209666; US, 2011. A 14-year old male died following an intentional suicide of acute drug poisoning with quetiapine. The patient experienced a tonic-clonic seizure, was intubated and placed on a ventilator, and suffered a fatal ventricular fibrillation cardiac arrest. Concomitant medication included bupropion.

ISR# 7211030; US, 2011. A 15-year old female died following intentional suspected suicide and acute drug poisoning with oral metoprolol, quetiapine, bupropion, amlodipine, amphetamine/dextroamphetamine, lamotrigine, and salicylate.

Toxicity to various agents

ISR# 6533709; US, 2010. A 15-year old female died following drug poisoning, pre-hospital cardiac arrest, and pre-hospital respiratory arrest with quetiapine.

ISR# 7171411; US, 2009. A 13-year old male received quetiapine to prevent future seizures, in addition to other unspecified medications. He experienced quetiapine toxicity and seizures, coma and death. The cause of death was toxicity to quetiapine; suicide was ruled out.

ISR# 7209757; US 2011. A 10-year old male died following a pre-hospital cardiac and/or respiratory arrest due to "acute malicious drug poisoning" with oral omeprazole, quetiapine, risperidone, clonazepam, lorazepam, alprazolam, valproic acid, atomoxetine, methylphenidate, and loratadine.

Overdose

ISR# 6802883; US 2010. A 12-year old male received quetiapine, olanzapine, clonazepam, and valproate for unknown indications and durations of therapy. He died from the events of "stopped breathing" and overdose.

ISR# 7357011; US 2011. A 4-year old female received quetiapine, valproate, and clonidine for unknown indications and durations of therapy. She died from an overdose.

Cardiac

ISR# 6541911; Foreign, 2010. A 13-year old female receiving quetiapine 300 mg daily for an unspecified indication and an unspecified duration was hospitalized while taking quetiapine. She developed cardiomyopathy subsequent to cessation of quetiapine while hospitalized, and died of cardiomyopathy.

ISR# 6822058; US, 2010. A 16-year old male treated with quetiapine died from a heart attack after an unknown duration of therapy. Concomitant drug or relevant medical history were not reported.

ISR# 6936013; Foreign, 2010. A 6-week old fetus who had been receiving transplacental quetiapine XR experienced cardiac arrest. The reporter stated that on a routine check, the gynecologist noticed that "the pregnancy stopped at 6-weeks development with a cardiac arrest of foetus". The gynecologist performed a curettage on the mother and a standard analysis of placental tissue was performed which revealed "anomalies on trophoblasts through (the) microscope."

Miscellaneous

ISR# 6486619; US, 2009. A 15-year old male with a history of respiratory symptoms, muscle rigidity, dysphasia, confusion, obsessive-compulsive disorder and Chiari malformation received quetiapine 900 mg daily for abnormal behavior. On an unspecified date, the patient developed bradycardia, brain death, electrocardiogram QT prolonged, electromechanical dissociation, hyperglycemia, hypoxic encephalopathy, hyperthermia, hypotension, *neuroleptic malignant syndrome (NMS)*, rash, and respiratory failure. He subsequently died because of the events. Concomitant medications included lithium and fluvoxamine, which are both labeled for an association with NMS.

ISR# 7110772; Foreign, 2010. A 16-year old patient received quetiapine, paroxetine, and lithium. The patient developed fatal liver failure, which was the cause of death.

ISR# 7194385; US, 2010. A 4-month old male died due to an unknown cause. The toxicology screen showed a quetiapine blood level of 170ng/mL and the presence of atropine. The mother of the child was not breast-feeding.

ISR# 7227596; US, 2011. An attorney reported that a 16-year old female died approximately five months after starting quetiapine. The death certificate reported the immediate cause of death as shock due to diabetic ketoacidosis and pancreatitis. Concomitant medications included clonidine, sertraline, olanzapine, carbamazepine, ondansetron, acetaminophen, xylocaine, lidocaine, dopamine, ranitidine, insulin, and norepinephrine. The autopsy reported anatomic findings of new onset diabetes mellitus, diabetic ketoacidosis, pulmonary congestion and edema, acute pancreatitis, hepatomegaly, ascities, and obesity. The case was confounded by a history of obesity and a family history of diabetes.

ISR# 7271854; US, 2005. An attorney reported that a 10-year old male with a congenital aortic valve defect, a leaky valve, and a medical history of four heart surgeries underwent aortic root homograft revision and subsequently developed multi-system end-organ failure culminating in cardiac arrest, and died. He received quetiapine 300 mg daily and risperidone for approximately two years. Concomitant medications included fluoxetine, amphetamine/dextroamphetamine, captopril, ramipril, and venlafaxine. The certificate of death listed the immediate cause of death to be "multiple organ system failure due to or as a consequence of ischemic cardiomyopathy, coronary artery stenosis and congenital heart disease."

ISR #7490088; US, 2011. An attorney reported that an 8-year old female died due to an unknown cause. At an unknown time prior to death, she took quetiapine 150 mg daily to treat somnambulism for an unknown duration. She experienced ketoacidosis,

pancreatitis, diabetes (reported as Type I and Type II), and peripheral neuropathy. She had a family history of diabetes. Concomitant medication included loratadine and methylphenidate.

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/s/

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12/01/2011

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12/01/2011

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