AstraZeneca

Safety Query Response

Drug Substance quetiapine fumarate

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Review of All Pediatric Reports For SEROQUEL® (quetiapine fumarate) Through 30 September 2004

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
Con med	Concomitant medication
CDS	Core Data Sheet
ICH	International Conference on Harmonization
KUR	Keep Under Review
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
Pt	Patient
PT	Preferred term
PSUR	Periodic Safety Update Report
SAE	Serious Adverse Event
SOC	System Organ Class
TTO	Time to onset

SUMMARY AND CONCLUSIONS

All available data for SEROQUEL involving the pediatric population was reviewed through 30 September 2004. This review included clinical trial and post-marketing data, and the medical/scientific literature. SEROQUEL is not approved for use in the pediatric population. The Children and Adolescents sub-section of Section 4.2 *Posology and Method of Administration* of the SEROQUEL Core Data Sheet (CDS) states the following:

> "The safety and efficacy of SEROQUEL have not been evaluated in children and adolescents."

A total of 65 reports (20 serious/45 non-serious) were identified from clinical trials with SEROQUEL, through 30 September 2004. No new significant safety issues were identified from a review of this data. Also, as of 30 September 2004, worldwide post-marketing reports received by AstraZeneca (AZ) comprised 840 reports for pediatric patients through 18 years of age. Assessment of causality was difficult in these cases because of incomplete clinical information, unclear temporal sequence of exposure and outcome, confounding by concomitant medications for which the event or related events have been reported, risk factors for the event, documented non-compliance, and/or alternative explanations. No new significant safety issues were identified from a review of the data. A review of the medical/scientific literature did not disclose any new significant safety issue for SEROQUEL

It was estimated that about 7.88 million patients worldwide (an estimate of almost 6.47 million patients in the United States (US) and 1.41 million patients outside the US) have been exposed to SEROQUEL for all time through June 2004 for the US and through first quarter 2004 for outside the US. This would include both pediatric and adult patients. The number of pediatric patients who had been exposed to SEROQUEL is available only for the US and is estimated (by the same process) to be 335,000.

Following a review of all the available relevant clinical and safety information, as well as the medical/scientific literature, it was determined that the data do not identify any significant new safety issues regarding the use of SEROQUEL in pediatric patients. The safety profile for SEROQUEL in the pediatric population is similar to the known safety profile for SEROQUEL in the adult population

AstraZeneca will continue to keep pediatric reports for SEROQUEL under careful review.

1. INTRODUCTION

The purpose of this document is to review all the available data for SEROQUEL involving the pediatric population and to assess if the safety profile for SEROQUEL in the pediatric population is similar to the known safety profile for SEROQUEL in the adult population. This paper includes a review of the clinical trial data, post marketing data, and the

medical/scientific literature regarding SEROQUEL use in the pediatric population, for all time through 30 September 2004. Following is a summary of the review.

2. BACKGROUND

2.1 SEROQUEL

SEROQUEL is an atypical antipsychotic agent, presented as tablets delivering a dose of 25 mg, 100 mg, 150 mg, 200 mg, or 300 mg of quetiapine free-base, which exhibits affinity for brain serotonin ($5HT_2$) and dopamine D_1 and D_2 receptors. It is this combination of receptor antagonism, with a higher selectivity for $5HT_2$ relative to D_2 receptors, which is believed to contribute to the antipsychotic properties and low extrapyramidal symptoms (EPS) associated with SEROQUEL. In comparative clinical trials, SEROQUEL has been shown to be as effective as standard antipsychotic agents such as chlorpromazine and haloperidol, but has a lower risk of causing EPS. A further benefit of reduced D_2 antagonism is that there are also fewer propensities to produce hyperprolactinemia, with the resultant effects of gynecomastia, galactorrhea, amenorrhea, menstrual disturbances and changes in libido. In addition, SEROQUEL also has high affinity at histaminergic and adrenergic α_1 receptors, with a lower affinity at adrenergic α_2 receptors, but no appreciable affinity at cholinergic, muscarinic or benzodiazepine receptors.

SEROQUEL is indicated for the treatment of acute and chronic psychoses, including both positive and negative symptoms of schizophrenia, and for the manic episodes in bipolar disorders.

SEROQUEL was first approved for marketing in the United Kingdom (UK) on 31 July 1997 and was first launched in the UK on 22 September 1997. By 31 July 2004, SEROQUEL has been approved in 82 countries for schizophrenia and in 42 countries for bipolar mania, with Mexico being the first country to approve bipolar mania on 29 May 2003.

2.2 Schizophrenia

Schizophrenia is a disorder that has a lifetime risk of approximately 1%, and it is one of the most debilitating and persisting diseases with 50 to 80% of initially discharged patients requiring re-hospitalization (Eaton et al 1992, Westermeyer and Harrow 1988).

Gastrointestinal cancer, cardiovascular disease, and infectious disease occur more often in the schizophrenic population than in the general population (Tsuang et al 1983). In addition, substance abuse is more common with a lifetime prevalence of alcoholism of 33.7% in people with schizophrenia compared to 13.5% in the general population (Vieweg et al 1995). While 30 to 35% of the general population smokes, the prevalence among schizophrenic patients is 75 to 92%. This high frequency may contribute to the increases in cancer and cardiovascular disease seen in schizophrenia (Gopalaswamy and Morgan 1986, Hughes et al, 1986, Masterson and O'Shea 1984). Likewise, the prevalence of diabetes mellitus (DM) is higher in

the schizophrenic population (10.8 – 14.9%/United States (US); Dixon et al 2000 and 15.8% Mukherjee et al 1996) than it is in the general population (7.3%/US; Mokdad et al 2001).

The mortality rate in schizophrenia is at least twice that of the general population, with suicides and accidental death being the most common causes of excess death (Vieweg et al 1995, Black et al 1985). More detailed epidemiological work has shown that there is a higher death rate due to infections (with tuberculosis being a major factor) and from cardiovascular disease, which may be in part related to the high prevalence of smoking in people with schizophrenia (Buda et al 1988).

Hussar studied autopsy reports in 1275 chronic schizophrenic patients (100% of whom were white men) between 1954 and 1959. The causes of death included heart disease (41.3%), cancer (13.1%), respiratory disease (17.4%), gastrointestinal disease (6.1%), vascular diseases other than stroke (5.3%), stroke (3.9%), urinary tract disease (1.6%), nervous system disease (1.3%), and other (10.2%). Thirty-one percent of the reviewed fatalities were diagnosed as experiencing "sudden death," mainly from myocardial infarction (Hussar et al 1966).

Buda et al (1988) followed 332 people with schizophrenia from first identification in the period 1934 to 1945 until 1974. In 1974, 124 (37%) were deceased. The cause of death was taken from the death certificate; 46 (37%) died of cardiovascular causes, 17 (14%) died of infections, 14 (11%) died of neoplasms, 6 (5%) committed suicide, 15 (12%) died of unnatural causes, and 32 (26%) died of other causes (unspecified).

The pattern of mortality and morbidity seen with patients with schizophrenia means that it can be predicted that AstraZeneca is likely to receive reports of cardiovascular, psychiatric (including suicides and sudden deaths), infectious and oncological AE reports, due to the patient population that will be receiving the drug.

Childhood-onset schizophrenia is a rare, clinically severe form of schizophrenia that is associated with disrupted cognitive, linguistic, and social development, which occurs before the appearance of psychotic symptoms (Jacobsen 1998). It has been estimated that 0.1% to 1% of patients with schizophrenia and its related disorders present before the age of 10 years, with 4% presenting before the age of 15 years (McClellan 2000).

2.2.1 Schizophrenia in children

The prevalence of schizophrenia in youth has not been adequately established. Clinical experience suggests that schizophrenia with onset prior to age 12 years is rare. It has been estimated that 0.1 to 1% of all schizophrenic disorders present before the age of 10, with 4% occurring prior to the age of 15. The rate of onset increases dramatically during adolescence, with the peak ages of onset ranging from 15 to 30 years (McClellan 2000).

2.3 Bipolar disorder

Bipolar disorder is a complex mental illness characterized by debilitating mood swings that range from intense euphoria to depression, interspersed with periods of relative stability. It is a lifelong disease, which affects between 1% and 2% of the world's population. Mortality

with bipolar illness averages two to two and a half times the expected rate for the patient's age. Twenty-five to fifty percent of patients attempt suicide at least once (Jacobson 2001) and completed suicide occurs in an estimated 8% to 15% of individuals with the disease; making it one of the most serious and deadly psychiatric illnesses. (Goldman 2000). In addition to the high risk of suicide, manic episodes in bipolar disorder are associated with depressive symptoms, psychosis, functional impairment, and agitated, aggressive and impulsive behavior that can require hospitalization.

Manic episodes range in severity from milder hypomania to delirious manic states that may include psychosis. The diagnostic criteria for a manic episode includes a distinct period of elevated, expansive, or irritable mood for at least one week or an event which requires hospitalization. Three of the following symptoms (four if mood only irritable) must be present: (1) inflated self esteem or grandiosity, (2) decreased need for sleep, (3) pressured speech, (4) flight of ideas or thoughts racing, (5) distractibility, (6) increased activity or (7) excessive involvement in pleasurable activities with a high risk of painful consequences. The occurrence also includes a marked impairment, psychosis or hospitalization and was not due to the direct effect of a substance or a medical condition. The diagnostic criteria for a hypomanic episode include a distinct period of elevated, expansive or irritable mood for at least four days. Three of the following symptoms (four if mood only irritable) must be present: (1) an unequivocal change in functioning, (2) a change observable by others, (3) episode not severe enough to cause a marked impairment, hospitalization or psychosis and/or (4) episode was also not due to the direct effects of a substance or a general medical condition (APA, DSM-IV, 1994).

2.3.1 Bipolar disorder in children

The diagnosis of pediatric bipolar disorder is on the rise; affecting an estimated 1% of children and adolescents (Lewinsohn et al 1995). One study (Goodwin et al 1990) suggested a peak age of onset between 15 and 18 years, however other studies (Lish et al 1994, Chang and Ketter 2001) suggests that significant mood or behavioral symptoms may occur many years before full criteria of bipolar disorder are present. Pediatric bipolar disorder often presents itself very differently from adult bipolar disorder. Adolescents with bipolar disorder may present with more mixed states and rapid cycling than adults with bipolar disorder (Geller et al 1995). Prepubertal presentations of mania may also present atypically, with briefer manic episodes or sustained conduct and impulse control problems (Wozniak 1995). Another example of age dependent presentation of bipolar disorder is the concurrent presentation of attention and behavioral disorders. Conduct disorder has been reported to be present in 69% of one cohort of adolescents with bipolar disorder (Kovacs et al 1995). The co-morbidity of attention deficit disorder (ADHD) with pediatric bipolar disorder is especially notable: researchers have reported up to 65% of adolescents and 94% of prepubertal children with pediatric bipolar disorder having co-morbid ADHD (Faraone 1997, West 1995).

2.4 Core data sheet

The AstraZeneca Core Data Sheet (CDS) is a summary of the company's position with respect to the essential scientific information, recommendations, and instructions needed for the safe

and effective use of the drug product. It serves as the master document for regular implementation of material changes in local prescribing information texts.

SEROQUEL has not been approved for use in the pediatric population. The Children and Adolescents sub-section of Section 4.2 *Posology and Method of Administration* of the SEROQUEL CDS states the following:

> "The safety and efficacy of SEROQUEL have not been evaluated in children and adolescents."

The *Pregnancy and lactation* section of the SEROQUEL CDS states:

> "The safety and efficacy of SEROQUEL during human pregnancy have not been established. Therefore, SEROQUEL should only be used during pregnancy if the benefits justify the potential risks… The degree to which quetiapine is excreted into human milk is unknown. Woman who are breast feeding should therefore be advised to avoid breast feeding while taking SEROQUEL."

2.5 Patient Exposure

By determining the total number of prescriptions of SEROQUEL sold (including refills for United States (US) and only new prescriptions for the rest of the world) and dividing that number by an estimated number of prescriptions that a patient takes in a lifetime (derived from proprietary market research), an estimate of worldwide patient exposure can be determined. It was estimated that about 7.88 million patients worldwide (an estimate of almost 6.47 million patients in the United States (US) and 1.41 million patients ex-US) have been exposed to SEROQUEL for all time through June 2004 for US and through first quarter 2004 for ex-US. This would include both pediatric patients and adult patients. The number of pediatric patients who had been exposed to SEROQUEL is available only for the US and is estimated (by the same process) to be 335,000.

2.6 Outline of this review

The medical/scientific literature is reviewed in section 3, or in section 6 (Topics of interest) if it is relevant to a topic of interest described in section 6. Reports from SEROQUEL clinical trials are discussed separately in section 4. The post marketing reports are discussed in section 5. The post marketing reports are separated into two groups; those that are medically confirmed versus those that are not medically confirmed. A medically confirmed report is one that came from a health care professional or that came from a consumer but was later verified by a health care professional. Reports that are not medically confirmed came from a consumer and were not able to be verified by any health care professional.

Every report is listed in one table and only one table in the post marketing section. Both the medically confirmed and the non-medically confirmed sections are organized similarly and are further sub-divided by the following age categories: 0 to 27 days (Newborns), 28 days to 23 months (Infants and Toddlers), 2 years to 11 years (Children) and 12 years to 18 years (Adolescents). Following of review of all reports (clinical trial and post marketing) in

sections 4 and 5, several topics were selected for further review in section 6 Topics of interest. For the Topics of interest, all relevant clinical trial data, post marketing reports, and medical/scientific literature for the particular topic were reviewed as an aggregate.

For section 5 (post marketing data) each report is listed in only one table and that is determined by its primary MedDRA preferred term. All secondary MedDRA preferred terms associated with a report are listed in the table as well. The primary preferred term is the first (primary) event reported for a patient and typically is the most serious event reported for the patient. All other events reported for a patient are considered secondary preferred terms. Each report is categorized (to one table) by its primary preferred term; it is listed in a table whose topic corresponds to the primary preferred term of the report. An analysis or summary of the reports in a table is presented below the table. In addition, for the sake of completeness, any other report not in the table, that had the topic reported at the secondary preferred term level, is also summarized in this section below the table.

In each age group, the tables are organized by topics. The first tables are of CDS listed topics and these are followed by the tables of CDS unlisted topics. The tables for CDS listed topics are first presented as serious topics for which there were multiple reports received, followed by serious topics for which there were only a single report received. Next, tables were created for reports of non-serious topics. The pattern is repeated for CDS unlisted topics. A report is grouped to a table by its topic and whether it is the only report of that topic (single report for topic) or one of several reports for that topic (multiple reports for topic). Seriousness at the report level does not influence what table a report is listed in; a report is listed in the table for the relevant topic and the topics are separated out by serious topics and non-serious topics. Therefore, it is possible for a non-serious report to be found in a table of a serious topic. For example, a report of overdose that was determined to be non-serious by the reporter would be listed in the table of overdose, and overdose is contained in a table of multiple reports for serious CDS unlisted topics, as overdose is considered a serious topic in this paper.

3. LITERATURE

A thorough search of medical databases (including Medline, Embase, Biosis, Current Contents) through 30 September 2004 was conducted to obtain information on literature articles about the use of SEROQUEL in pediatric patients. In summary, no new significant safety issues were identified from a review of the data. Following is a summary of the relevant information.

3.1 Weight gain

See section 6.5 *Topic of interest; Weight gain* for relevant literature.

3.2 Prolactin

See section 6.11 *Topic of interest; Hyperprolactinemia and related adverse events* for relevant literature.

3.3 Glucose dysregulation

See section 6.2 *Topic of interest; Glucose dysregulation* for relevant literature.

3.4 Newborns

Use of quetiapine in a nursing mother was reported in an abstract (Lee et al 2004). Measurements on the excretion of quetiapine in breast milk were taken from a 36-year-old (92.5 kg) woman who had given birth to a healthy full term baby and wished to continue treatment with SEROQUEL and breast-feed her infant. Manually expressed breast-milk samples were collected over a six-hour period at three weeks postpartum. Samples were obtained just before the SEROQUEL dosing and again at one, two, four, and six hours post dose. Samples were stored in the appropriate manner and high-performance liquid chromatography analysis was performed by using 1500 mm of C18 column Kromasil. The area under the curve of SEROQUEL in breast milk from time 0 to 6 hours was calculated by using the trapezoidal method. The elimination half-life of SEROQUEL in breast milk was calculated by using the log-linear elimination phase of the drug. The daily amount of SEROQUEL ingested by a nursing infant was calculated by assuming that an infant ingests 150 ml/kg/day of breast milk and by using the average milk concentration of SEROQUEL over six hours. The maximum amount an infant will ingest was calculated based on the highest milk concentration. The average milk concentration of quetiapine over the six hours was 13 µg/L, with a maximum concentration of 62 µg/L at one hour. Levels of SEROQUEL rapidly fell to almost pre-dose levels by two hours. Therefore, an exclusively breast fed infant would ingest only 0.09% of the weight adjusted maternal dose. At maximum, the infant would ingest 0.43% of the weight adjusted maternal dose. Upon receiving the results of levels in the breast milk, the woman began breast-feeding exclusively at eight weeks after delivery. Follow-up of the infant at 4.5 months indicated that the infant was developing well, and no AEs for SEROQUEL were reported.

3.5 Other studies

An eight-week, open trial using SEROQUEL (entitled *A Study of qQuetiapine: Efficacy and Tolerability in Psychotic Adolescents*) in 15 adolescents (ages 13-17 years; mean=15.1 years) with psychotic disorder focused primarily on psychotic symptomology but other measures included AEs, clinical laboratory tests, vital signs, electrocardiograms (ECG) extrapyramidal measures, and ophthalmologic examination. The SEROQUEL dose ranged from 300 to 800 mg/day (mean final treatment dose=467 mg/day). No patients withdrew from the study due to AEs from SEROQUEL. The AEs noted during the trial were somnolence (4 patients), headaches (4 patients), and agitation (1 patient). No evidence of ophthalmologic changes was found between baseline and the conclusion of the study. Changes in systolic and diastolic blood pressure and pulse rate over the 8-week period were not significantly different. T_4 levels decreased while thyroid stimulating hormone levels increased over the 8-week trial; these findings were not significant. Mean cholesterol levels increased only slightly from baseline to discharge (mean at baseline=156.9 [SD=30.5], mean at 8 weeks=161.9 [SD=34.2]). Prolactin levels slightly decreased from a mean of 11.3 ng/mL to a mean of 11.1 ng/mL (after omitting one patient who had begun hormonal treatment for a gynecological

problem). A review of ECGs before and after the 8-week period failed to reveal any significant changes in electrocardiographic parameters, specifically for the P-R interval, QRS complex, and QT interval. The initial average weight of all subjects was 71.5 kg (SD=21.6) and at discharge the mean weight was 75.6 kg (SD=22.8). A significant difference was found for the change in weight from baseline to week 8. After correction for expected weight gain for boys and girls, the mean weight gain for the entire sample was 3.41 kg for the 8-week period. It was also noted by the authors that SEROQUEL significantly improved psychotic symptomology and was not associated with EPS of the course of the trial (Shaw et al 2001).

A total of 10 female and male patients aged 12.3 to 15.9 years and weighing between 48.2 and 95.5 kg were enrolled in an open label, rising- and multiple-dose, tolerability, and pharmacokinetic trial (entitled *Tolerability and pharmacokinetics of SEROQUEL in adolescents with selected psychotic disorders*) and received oral doses of quetiapine twice daily, starting at 25 mg twice a day and reaching 400 mg twice a day by day 20. The trial ended on day 23. To be eligible for this study, patients had to have a chronic or intermittent psychosis with a documented clinical diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, major depressive disorder, or bipolar disorder (as defined in DSM-IV). A history of tolerability to antipsychotic treatment was a criterion for participation; however, use of depot formulation antipsychotics within one dosing interval before trial entry was not permitted, nor was current treatment with clozapine. Similarly, the use of drugs known to alter or induce metabolic enzymes, including barbiturates, carbamazepine, thioridazine, or phenytoin, was not permitted within six weeks of trial entry. Patients who took lithium for underlying psychiatric disorders were on a stable dose for at least one month before participating in the trial. Primary exclusion criteria included patients with alcohol or psychoactive substance dependence not in full remission, a positive test for drug abuse or pregnancy, and any clinically significant medical conditions that could affect required evaluations or increase the risk of adverse effects with treatment. Patients were divided into two groups determined by age; one group included 12 through 14 year olds and the other group 15 through 17 year olds. All patients completed the trial. Adverse events were mild to moderate, with no serious events reported during treatment. The authors concluded that quetiapine was well tolerated in adolescents in this trial. No new safety issues arose during therapy, and the side effect profile of quetiapine in adolescents was similar to that in adults. The occurrence of postural tachycardia (9 of 10 patients) may have reflected reflex tachycardia in response to orthostatic hypotension. Clinical laboratory test findings were consistent with those observed for adults who were treated with quetiapine. As in adults, small decreased in mean total and free T_4 were observed; however, the decrease in T_4 was not accompanied by a concomitant increase in thyrotropin (TSH). Moreover, all patients were asymptomatic, and no event was associated with clinical hypothyroidism. Prolactin levels were not adversely affected by quetiapine therapy. The lack of sustained serum prolactin elevations in adolescents corroborates findings from studies in adults. Neurologic evaluations indicated that quetiapine, unlike standard antipsychotic agents did not induce EPS. In fact, mean Simpson-Angus Scale and BAS scores decreased over the course of therapy, indicating improved EPS. Also, no patients required treatment or withdrew from the trial because of EPS. Clinically, quetiapine improved both positive and negative symptoms in the chronically ill adolescent patients studied. This trial was limited by several design factors such as the

small number of patients, the open-label nature of the study, inclusion of various diagnostic categories, and patients' previous exposure to a number of antipsychotic medications. However, the authors noted that these preliminary results indicate that quetiapine given within the recommended treatment range for adults has a pharmacokinetic and safety profile similar to that for adults (McConville et al 2000). In a long-term extension of this trial (mean total duration=455 +/- 155 days) there were not elevated prolactin levels or evidence of cataracts. Weight gain varied, however many patients were noted to be on concomitant therapy with known weight gain potential. In addition no EPS or evidence of tardive dyskinesia (TD) were seen (McConville 2001; the main study was presented in a full article but the long term extension results was presented in an abstract only).

One prospective study titled *Safety, tolerability, and efficacy of quetiapine as adjunctive treatment for bipolar adolescents with mania* (published in abstract form) involved 30 manic adolescents (ages 12 to 18). At the time of the abstract 22 patients had completed the study. Patients were randomized to SEROQUEL and divalproex or placebo and divalproex for six weeks. All received a maximum SEROQUEL dose of 450 mg/day. According to the blinded pooled data, the most common AEs were headache (55%), nausea and vomiting (55%), and sedation (45%). Most AEs were mild; no serious AEs occurred. No EPS, QTc prolongation, orthostatic hypotension, or significant changes in laboratory tests were noted. Mean change in prolactin was -1.9 ± 8.7 ng/ml. The authors concluded that preliminary analyses of the blinded, pooled data suggest that SEROQUEL is safe and well tolerated as adjunctive therapy to divalproex in manic or mixed adolescents with bipolar disease (DelBello et al 2001).

Ten children and adolescents (aged 6 to 14 years) with ADHD and aggression that inadequately responded to a psychostimulant were given SEROQUEL in an open, uncontrolled, prospective study entitled *An open trial of quetiapine for aggression in children and adolescents with attention deficit hyperactivity disorder*. The maximum dose was 200 mg/day. The results indicated that addition of SEROQUEL to psychostimulant therapy resulted in significant reductions in aggression scores. No serious side effects requiring discontinuation of therapy were observed. The most common AEs included sedation and fatigue observed in three patients. The authors (Kehoe et al 2002) concluded that SEROQUEL was effective for reducing aggression in children and adolescents with ADHD when psychostimulants were inadequate. It was well tolerated with no serious side effects noted.

A study entitled *Open-label Quetiapine in the Treatment of Children and Adolescents with Autistic Disorder* was designed as a 16-week, open-label trial that included six male subjects with autistic disorder that functioned in the mentally retarded range (mild n=2; moderate n=3; severe n=1) (Martin et al (1999)). Only two subjects completed 16 weeks of treatment. Dosages ranged from 100 to 350 mg/day. Subjects dropped out prematurely because of lack of response and sedation, limiting further dose increased (n=3), and because of a possible seizure during the fourth week of treatment (n=1). Other AEs included increase appetite (n=4) and weight gain (n=4; mean=2.9 ± 3.6 kg). Although weight gain was described as substantial in four patients, mean weight gain was not statistically significant for the six subjects as a group (p=0.15). When observed, however, appetite and weight increase emerged during the

first four weeks of treatment. The authors concluded that SEROQUEL was poorly tolerated and ineffective in most subjects in this sample; and that side effects were significant and seriously limited the use and dosing of the medication. However, the study must be considered in light of methodological limitations, most notably a small sample size in a very specific population and an open-label design lacking a placebo control group.

An open study (*New antidepressive and antipsychotic drugs in juvenile neuronal ceroid lipofuscinoses--a pilot study)* consisted of 14 Finnish patients (two males, 12 females) with juvenile neuronal ceroid lipofuscinoses, receiving psychotropic drug treatment. The mean age of the patients at initiation of the new antidepressants or new antipsychotics was 13.8 years (range 7 to 25; all patient but one under the age of 18). The psychotropic agents used were citalopram, risperidone, olanzapine, and SEROQUEL, either as monotherapy or in combinations. The mean maintenance dose of SEROQUEL was 200 mg/day. Ten patients were treated with citalopram, six with risperidone, three with olanzapine, and one with SEROQUEL. The one patient treated with SEROQUEL was switched from olanzapine to SEROQUEL during the study due to lack of response and marked increase in EPS. The AEs most commonly reported (for all therapies) were fatigue, weight gain, and EPS (SEROQUEL patient experienced agitation and wakefulness). It was reported by the authors that the most common treatment of JCNL in Finnish patients is risperidone and/or citalopram. SEROQUEL was tried in only one patient but had remarkable effect. This patient had severe psychotic symptoms including agitation, delusions, and hallucinations, for several years. Several psychotropic drugs were tried without success (Backman et al 2001).

Following a review of this medical/scientific literature, it was determined that no new significant safety issues specific to the use of SEROQUEL in neonates, children, or adolescents were identified.

4. CLINICAL TRIALS (65 REPORTS)

A total of 65 reports (20 serious/45 non-serious) were identified from clinical trials with SEROQUEL. These reports are reviewed below. The non-serious clinical trial reports are listed in Appendix A.

4.1 All serious reports (20 reports)

4.1.1 CDS Listed Topics (2 reports)

There were no multiple serious clinical study reports for any CDS listed topics.

Two single serious clinical study reports were received for two separate CDS listed topics. These are contained in Table 1 below.

Table 1 Single Report for CDS listed Topic (2 reports)

Topic	Report	Age /Sex	Primary preferred term	Serious	Investigator Causality (Y/N)	Secondary preferred terms	Serious	Investigator Causality (Y/N)
Leukopenia	ACH-5077-02/1 (2003PK02057)	17/ M	Leukopenia	Yes	Yes	None	NA	NA
Syncope	AU-SEA-0005 (2004AP02095)	15/ F	Syncope	Yes	Yes	None	NA	NA

Summary for single reports for CDS listed topics: The AEs reviewed above are listed in the SEROQUEL CDS for the adult population. Following a review of these reports, it was determined that there was no difference in frequency, severity or characteristics of these events when compared to the known profile of SEROQUEL in adults.

4.1.2 CDS Unlisted Topics (18 reports)

The reports associated with CDS unlisted topics for which multiple serious clinical study reports were received are listed in Table 2 below.

Table 2 Multiple serious clinical study reports for serious CDS unlisted topics (10 reports)

Topic	Report	Age/ sex	Dose/ TTO	Medical history	Concomitant medication	Comment/ Investigator causality
Suicidal and self-injurious behavior[a]	5077/9025-01/005 (2002PK00588)	18/M	800 mg /day/26 days	Depression, schizophrenia	Lorazepam	PTs: Suicide attempt. Suicide attempt (strangulation) while hospitalized. Clinical sxs not reported. Seroquel stopped; Pt withdrawn from study. Pt rec'd. Investigator causality=not related.
	D1441C00028-0002/2201 (2004UW09891)	13/F	Dose/ TTO unk	Psychosis	Not provided.	PTs: Suicide attempt. Suicide attempt (strangulation and superficial scratches on wrist) while hospitalized. No LOC. Outcome unk. Seroquel stopped; Pt withdrawn from study. Investigator causality=not related.
	AU-SEA-0005-01/006 (2004AP02997)	15/F	600 mg /day;58 days	Schizophreniform psychosis, depression, acne	Risperidone, erythromycin, doxycycline, venlafaxine, sertraline	PTs: Depression suicidal. Depressed + suicidal (suicidal ideation). Has command hallucinations instructing self-harm + suicide. Hospitalized. Seroquel dosage increased and Pt treated w/venlafaxine and sertraline. Pt improved; was discharged. Investigator causality=not related.
	AU-SEA-0005 01/006 (2004AP02999)	15/F	Dose unk;84 days	Schizophreniform psychosis, depression, acne	Risperidone, erythromycin, doxycycline, venlafaxine, sertraline	PTs: Persecutory delusion, intentional self-injury. Pt re-hospitalized w/persecutory delusions and intentional self-injury (unspecified). Seroquel dosage increased. Pt rec'd. Investigator causality=not related. Same Pt as AU-SEA-0005-01/006 above.
Behavior and socialization disturbances[b]	5077IL/0107- 609/0003 (2001SE06512)	18/M	400 mg /day;66 days	Schizophrenia, conduct disorder, agitation, drug dependence	Chlorazepate	PTs: Aggression. Pt frightened girlfriend by throwing things; police intervention took place at home. Pt rec'd. Seroquel contd at same dose. Investigator causality= not related. Non-serious event included worsening agitation.
	ACH-5077-02/1-01-06 (2003SE01290)	17/F	300mg/ day; 61 days	Psychosis, aggressive behavior, sexual abuse	Sertraline	PTs: Aggression. Pt was aggressive toward a teacher and had persistent delusional ideas of persecution. Unknown if Pt rec'd; Pt contd in study. Investigator causality= not related for Seroquel. Sertraline=related.
	ACH-5077-02/1-01-03 (2003SE00175)	17/M	400mg/ day; 69 days	Alcohol + cannabis abuse, Paranoid schizophrenia.	None	PTs: Aggression. Pt was violent at home because of persecutory ideas. He was imprisoned. Seroquel not taken regularly. Pt rec'd. Seroquel contd. Investigator causality=not related.

Table 2 Multiple serious clinical study reports for serious CDS unlisted topics (10 reports)

Topic	Report	Age/ sex	Dose/ TTO	Medical history	Concomitant medication	Comment/ Investigator causality
Behavior and socialization disturbances[b]	5077US-0024/0001-0023 (2001UW08245)	18/M	400mg/ 1day; 5 days	Psychosis	Olanzapine	PTs: Hostility. Investigator-initiated trial. Pt had no history of violent behavior, was hospitalized for making violent threats. Tapered off olanzapine during titration of study med. Pt had not rec'd at time of report. Seroquel contd. Investigator causality=related.
Exacerbation of psychiatric disorders	ACH-5077-02/1-01-03 (2002SE06089)	17/M	400mg/ 6 days	Psychosis, cannabis use	None provided.	PTs: Delusional disorder, persecutory type. Pt hospitalized for worsening sxs. Urine screen cannabis +. Seroquel contd. Unk outcome. Investigator causality=not related for Seroquel. Cannabis=related.
	ACH-5077-02/1-01-10 (2004PK00262)	17/M	Unk/3 days	Psychosis, anxiety, cannabis use	lorazepam	PTs: Psychotic disorder. Pt had exacerbation of psychotic sxs after tapering off zuclopenthixol. Seroquel ↑ and levomepromazine added. Outcome unk. Investigator causality=not related. Investigator stated causality possibly related to cannabis + discontinuation of zuclopenthixol and sxs not controlled by Seroquel starting dose.

[a,b] see sections 6.3, 6.13, respectively for more information, sxs=symptoms, rec'd=recovered, unk=unknown, LOC=loss of consciousness, w/=with, contd=continued.

Summary for multiple reports for CDS unlisted topics: The four reports of suicidal and self-injurious behavior (2002PK00588, 2004UW09891, 2004AP02997, 2004AP02999) will be discussed in section 6.3 *Topics of interest; Suicide*. The next four reports of behavior and social disturbances will be discussed in section 6.13 T*opics of interest; Behavioural disturbances*. Of the two reports of psychiatric disorder, the first report (2002SE06089; delusional disorder persecutory type) was confounded by cannabis use, and the second report (2004PK00262) was confounded by possible cannabis use and a low SEROQUEL starting dose while the patient was tapered off of zuclopenthixol.

Following a review of this data it was determined that the data do not establish a causal relationship between SEROQUEL and suicide, behavioral disturbances, and exacerbation of psychiatric disorders.

The serious clinical study reports for CDS unlisted topics for which only a single report was received are contained in Table 3 below.

Table 3 Single serious clinical study reports for CDS unlisted topic (8 reports)

Topic	Report	Age/ sex	Primary PT	Serious	Investigator Causality (Y/N)	Secondary PTs	Serious	Investigator Causality (Y/N)
Normal newborn	5077IL/0061/0001/0113 (1998AP44719)	18/F	Normal Newborn	N	N	None	NA	NA
Tumor excision	AU-SEA-0005/01-006 (2004AP03668)	15/F	Tumour excision	Y	N	None	NA	NA
Ovarian cyst pain	5077US/0049/0023/1301 (2003UW097820)	18/F	Adnexa uteri pain	Y	N	Dysmenorrhea Nausea	N N	N N
Cellulitis	5077IL/0038/0001/0103 (1999UW01047)	15/F	Cellulitis	Y	N	Tachycardia Hypothyroidism Dizziness Somnolence Insomnia Electrocardiogram abnormal Thrombocytopenia Dysmenorrhea Otitis external Headache Pharyngitis Cough increased	N N N N N N N N N N N N	Y Y Y Y N Y Y N N Y N N
Muscle disorder	5077CN/0009-0001 (2001UW00762)	18/ M	Cataplexy	Y	Y	Tic	N	Y
Headache	5077IL/0038/0001/0101 (1999UW00377)	15/ M	Headache	Y	Y	Blurred Vision Vomiting Fever Tachycardia Headache Weight increase Thirst Flu syndrome Reaction unevaluable	Y Y Y N N N N N N	Y Y Y Y N N N N N
Pseudo-tumor cerebri	5077IL/0038/0001/0101 (1997AP35013)	14/ M	Benign intracranial hypertension	Y	Y	Same as above	NA	NA
Anxiety	5077IL/0051/0311/0002 (1998AP44436)	17/F	Anxiety	Y	N.	None	NA	NA

Summary for single reports for CDS unlisted topic: For the events of normal newborn (non-serious), tumor excision, ovarian cyst pain, cellulitis, muscle disorder, headache, pseudotumor cerebri and anxiety, the reports involved a single report for each event (or topic). Therefore, no trends could be identified from these reports.

4.2 All non-serious clinical study reports (45 reports)

Non-serious clinical trial reports are not contained in the AstraZeneca safety database Clintrace (see section 5.1 about Clintrace), therefore, there is no preferred term hierarchy associated with these reports. The non-serious clinical trial reports are summarized in Appendix A. In addition, all events contained in the non-serious clinical study reports were assessed for CDS listedness and summarized in Table 4 (listed events) and Table 5 (unlisted events) below.

Table 4 CDS listed events from non-serious clinical study reports

Event	Number of events reported
Akathisia	1
Asthenia	10
Constipation	3
Dizziness	15
Dry mouth	3
Dyspepsia	5
Eosinophilia	1
Face edema (angioneurotic edema)	1
Gamma glutamyl transpeptidase increased	1
Heart rate increased	3
Hypothyroidism (Low T3-T4)	5
Increased salivation (drooling)	1
Leukopenia	13[a]
Orthostatic hypotension	1
Rhinitis	5
Sedation	2
SGOT increased	2
SGPT increased	4
Somnolence	25
Syncope	1
Tachycardia	19
Tremor	2
Weight increased	8
Total number of events	132

[a] Leukopenia events were coded using the Costart dictionary. The PT of leukopenia included the lower level terms of neutropenia and leukopenia. Of the 13 reports of leukopenia, 7 were of neutropenia. Twelve of the 13 events of leukopenia resolved while SEROQUEL was continued. One report of leukopenia had no outcome and described a decreased white blood cell count ($3.9x10^9$/L) with a normal neutrophil count (2.1 x 10^9/L) in a patient who had received SEROQUEL for four days.

Table 5 CDS unlisted events from non-serious clinical study reports

Preferred term	# of AEs	# AEs where investigator causality=Yes	Preferred term	# of AEs	# AEs where investigator causality=Yes
Abdominal pain	4	0	Infection	4	0
Accidental injury	6	0	Infection bacterial	1	0
Agitation	14	4	Infection fungal	1	0
Alkaline phosphatase increased	2	2	Injection site pain	1	0
Alopecia	1	0	Insomnia	17	9
Anemia	2	0	Lab test abnormal	1	0
Anorexia	1	0	Lymphadenopathy	2	0
Anxiety	8	1	Malaise	1	0
Aphthous stomatitis	1	0	Melena	1	0
Appetite increased	1	1	Mood swings	1	0
Arrhythmia	2	0	Myalgia	1	0
Arthrosis	1	Unk	Nausea	5	0
AV Block	1	0	Nervousness	3	1
Back pain	3	0	Otitis external	1	0
Blood pressure diastolic decreased	1	1	Pain in extremity	1	0
Blood pressure systolic decreased	1	1	Pericarditis	1	0
Bronchitis	1	0	Pharyngitis	18	0
Chest pain	1	0	Prolactin increased	1	0
Conjunctivitis	1	0	Rash	2	1
Cough increased	2	0	Reaction unevaluable	2	1
Diarrhea	3	0	Sinus congestion	1	0
Disturbance in attention	1	1	Sinusitis	2	0
Dysmenorrhea	4	0	Sluggishness	1	1
Dysuria	1	0	Stomatitis	1	0
Ear pain	2	0	Sweating	1	1
Ecchymosis	1	0	Tension headache	1	0
Electrocardiogram abnormal	5	4	Thirst	1	0

Table 5 CDS unlisted events from non-serious clinical study reports

Preferred term	# of AEs	# AEs where investigator causality=Yes	Preferred term	# of AEs	# AEs where investigator causality=Yes
Emotional lability	1	0	Thrombocytopenia	1	1
Fatigue	4	4	Tic	1	1
Flu syndrome	4	4	Tinnitus	1	0
Gastritis	3	0	Twitching	1	0
Generalized edema	1	0	Urinary incontinence	1	0
Gum hemorrhage	1	0	Urinary retention	1	Unk
Headache	28	3	Urinary tract infection	1	0
Hostility	1	1	Vasodilatation	2	2
Hypertension	4	4	Vision blurred	2	2
Hyperthyroidism	1	1	Vomiting	6	2
Hypotension	1	0	Weight decreased	2	0

Total number of events: 212 (total considered related by investigator = 50)

There were 344 non-serious events for 50 clinical study patients (five of these are serious reports) participating in 26 studies. Five of the 50 patients also had serious events and are counted/listed in section 4.1 above. However, the non-serious AEs associated with these five serious reports are discussed/counted in this section (section 4.2). Of the 344 non-serious events, 132 were CDS listed events and 212 were CDS unlisted events. The number of days on study drug (SEROQUEL), including randomized and open-label extension (OLE) phases ranged from three days to three years 149 days. The mean number of days on study drug was 221 days and the median was 58 days. Nine patients completed an open-label portion of the trials.

Following is a summary of non-serious unlisted events for which there were five or more occurrences. Five patients had six events of "Accidental injury." No pattern could be determined, and none were considered related to SEROQUEL therapy. Eight patients had 14 events of "Agitation." Of these 14 events of agitation, eight were confounded by a history of agitation, one event of agitation had a verbatim term of panic attack and five had scant clinical detail and did not lend themselves to analysis. Four events of "Agitation" were considered causally related to SEROQUEL therapy.

Five patients had eight events of "Anxiety." Of these eight events of anxiety, five were confounded by a history of anxiety and three had scant clinical detail and did not lend themselves to analysis. One event of "Anxiety" was assessed as causally related to SEROQUEL therapy.

Five patients (all from the same investigator and the same site) had five events of "Electrocardiogram abnormal." See Section 6.6 *Topics of interest; Prolonged QT* for details

of these reports. Taken together, the data is insufficient to establish a causal relationship between prolonged QT and the use of SEROQUEL in children.

Seventeen patients had 28 events of "Headache." One headache occurred coincident with sinusitis but the rest of the events had scant clinical detail, and did not lend themselves to analysis. Three events of "Headache" were assessed as causally related to SEROQUEL therapy, by the investigator.

Thirteen patients had 17 events of "Insomnia." The 17 events of insomnia had scant clinical detail and did not lend themselves to analysis. Nine events of "Insomnia" were assessed as causally related to SEROQUEL therapy, by the investigator. Four patients had five events of "Nausea." These five events had scant clinical detail and did not lend themselves to analysis. None of the events of "Nausea" were assessed as causally related to SEROQUEL therapy, by the investigator. Eight patients had 18 events of "Pharyngitis." Twelve events of pharyngitis had the verbatim term of head cold, three had the verbatim term of upper respiratory infection, two had the verbatim term of sore throat, and one had the verbatim term of tonsillitis. None of the events of "Pharyngitis" were assessed as causally related to SEROQUEL therapy, by the investigator.

One patient, with a history of a hypertensive event five days before starting study drug, had four events of "Hypertension." No blood pressure readings were provided. These four events of "Hypertension" were assessed as causally related to SEROQUEL therapy, by the investigator. Five patients had six events of vomiting. These events had scant clinical detail and did not lend themselves to analysis. Two of the events of "Vomiting" were considered causally related to SEROQUEL, by the investigator.

Following a review of the non-serious unlisted events for which there were five or more occurrences, it was determined that no new significant safety information about the use of SEROQUEL in children was identified.

5. CLINTRACE DATABASE (IN HOUSE SAFETY DATA)

5.1 General

The AstraZeneca safety database (Clintrace) contains marketed AE reports, both foreign and domestic, from consumers, health care professionals, registries, clinical trials, and literature articles for SEROQUEL. For clinical trials, only reports associated with a serious AE are included. The following summary is based on information in Clintrace through 30 September 2004.

5.2 Clintrace search strategy

A comprehensive search of Clintrace was performed to identify reports that pertained to children and adolescents. Any report involving a patient with an age of 0 to 18 years or an age category designated as neonate, infant, child, or adolescent was included. In addition, any

report identified by a narrative search for select words indicating a newborn, child, or adolescent were reviewed and included if they identified a newborn or child or adolescent.

5.3 Clintrace results (840 reports)

A total of 840 reports were identified from the search. Of these, 724 were medically confirmed (discussed in section 5.4 below) and 116 were not medically confirmed (discussed in section 5.5 below). Of the medically confirmed reports, 30 reports were received for the age 0 to 27 days group (Newborns), two reports were received for the age 28 days to 23 months group (Infants and Toddlers), 199 reports were received for the age 2 to 11 years group (Children), and 493 reports were received for the age 12 to 18 years group (Adolescents). Of the non-medically confirmed reports, two reports were received for the age 0 to 27 days group, one report was received for the age 28 days to 23 months group, 36 reports were received for the age 2 to 11 years group, and 77 reports were received for the age 12 to 18 years group.

5.4 Medically confirmed reports (724 reports)

5.4.1 Newborns (age 0 to 27 days; 30 reports)

5.4.1.1 CDS listed topics (0 reports)

There were no reports received by AZ that contained a primary preferred term, which referred to a topic that is listed in the SEROQUEL CDS for this age group.

5.4.1.2 CDS Unlisted topics (30 reports)

Multiple reports for serious CDS unlisted topics

The reports associated with CDS unlisted topics for which there was multiple reports are contained in Table 6 below.

Table 6 Multiple reports for serious CDS unlisted topics (15 reports)

Topic	Report	Age/ Sex/ Wt	Dose/ Duration	Mother's medical History	Concomitant medications	PTs/Comments
Premature baby	1999AP06076 Serious	31 wks/ F/ 2 kg	450 ↓ to 400 mg/day; duration unk	Gestational DM	Droperidol, fluoxetine[a], insulin, procylidine, chlorpromazine	PTs: Premature baby, Convulsion neonatal, Hypotonia neonatal, Sepsis neonatal, Feeding problem in newborn. Needed ventilation @ birth, had hypotonia, twitching, clonic movements of all limbs. Day 9 of life: septicemia, seizures. Tx=phenobarbitone (until day 32 of life), phenytoin (until day 26 of life), clonazepam. EEG (Day 5 + 9 of life)=abnormal background w/ period of suppression, maybe d/t meds. Cranial US + metabolic investigations WNL. Feeding problems d/t prematurity. Not feed orally until Day 42 of life. Baby rec'd w/ sequelae from prematurity + rec'd/rec'g from hypotonia, twitching. Outcome unk for seizures, septicemia.
	2004AP04599 Serious	35 wks/ M/2.24 kg	Dose/ duration unk	Not provided	Methadone	PTs: Premature baby, Neonatal disorder Mother had short cervix w/ early dilation + spontaneous premature labor. NB had neonatal complications d/t prematurity + neonatal obstinance syndrome. Outcome unk. No other info.
	2004UW17483 Serious (2004UW17484 same mother; second baby)	37 wks/ sex + wt unk	75 mg/day; entire pregnancy	No drug or alcohol abuse, no smoking	Sertraline, vitamins	PTs: Premature baby, Neonatal respiratory distress syndrome, Developmental delay. NB w/ "floppy baby" + respiratory distress requiring neonatal care. Later had developmental delays, including not walking until 14 mos of age. Rec'd from premature birth, respiratory distress. Not yet rec'd from developmental delay. (first baby)
	2004UW17484 Serious (2004UW17483 same mother; first baby)	33 wks/ M/wt unk	≤75 mg/day; entire pregnancy	Pre-term labor, no drug or alcohol abuse, no smoking	Sertraline, vitamins	PTs: Premature baby, Neonatal respiratory distress syndrome. NB had neonatal respiratory distress. NB rec'd + discharged to home. (second baby)
Neonatal drug withdrawal	2002GB02909 Serious	Age, sex, wt unk	400 mg/day; entire pregnancy	Not provided	Diazepam[b], fluoxetine[b]	PTs: Drug withdrawal syndrome neonatal NB had drug withdrawal syndrome immediately after delivery. No tx. Baby rec'd. No other info.

Table 6 Multiple reports for serious CDS unlisted topics (15 reports)

Topic	Report	Age/ Sex/ Wt	Dose/ Duration	Mother's medical History	Concomitant medications	PTs/Comments
	2004UW03627 Serious	Age unk/F/ wt unk	1000 mg/day; duration unk	Not provided	Not provided	PTs: Drug dependence; Tremor Baby born w/ "shakes." Mother tested negative for cocaine. Outcome unk. No other info.
Neonatal drug withdrawal	2003AP03328 Non-serious	Age unk/F/ 4 kg	1000 mg/day; duration unk.	Not provided	Amisulpride, coloxyl w/ senna, multivitamins	PTs: Drug withdrawal syndrome neonatal, Agitation neonatal, Hypertonia, Feeding problem in newborn Day 1 of life: jittery w/ hypertonicity, poor feeding. Dx=withdrawal syndrome w/ Seroquel. Baby rec'd on unk date. No other info.
	2001AP03788 Non-serious	Age unk/F/ wt unk	Dose/ duration unk	Opiate & benzodiazepine dependence	Methadone, diazepam[b], sulpiride, venlafaxine[b], lofexidine	PTs: Drug withdrawal syndrome neonatal, Normal newborn. Baby had slight withdrawal sxs. Rec'd in one wk. No other info.
Congenital disorders	2003GB00079 Serious	Full term/F/ 3.12 kg	200 mg/day; 1st trimester only	Anxiety, panic, psychosis, normal pregnancies (2), ex-smoker (6 y ago), no alcohol during pregnancy	Cephadrine x 5 days (≈38 wks gestation)	PTs: Congenital ventricular septal defect, Transient tachypnea of the newborn. Mother treated for UTI ≈38 wks gestation. NB had transient tachypnea & VSD of 4 mm. No intervention for VSD. Outcome unk. No other info.
	2000AP01959 Serious	Age unk/F/ 3 kg	250 mg/day; duration unk	Not provided	Lorazepam, zoplicone, trazodone, perphenazine, citalopram, methotrimeprazine	PTs: Respiratory tract malformation, Neonatal disorder Neonate w/ hypotonia + respiratory depression requiring mechanical ventilation. At 6 wks old: Respiratory center depression w/ alveolar hypoventilation. Dx: Congenital hypoventilation syndrome. NB also had unspecified eye abnormality. Baby not yet rec'd from events. No other info.

Table 6 Multiple reports for serious CDS unlisted topics (15 reports)

Topic	Report	Age/ Sex/ Wt	Dose/ Duration	Mother's medical History	Concomitant medications	PTs/Comments
	2003PK01557 Serious	Full-term/F /wt unk	400 ↓ to 300 mg/day; until 24 wks gestation	Cannabis abuse, tobacco use, varicella infection at 26 wks gestation	olanzapine	PTs: Cleft lip, Hyperbilirubinemia neonatal, Hypoglycemia neonatal Tx + outcome of mother's varicella infection unk. Baby born w/ cleft lip, hyperbilirubinemia, hypoglycemia. Outcome for hyperbilirubinemia + hypoglycemia unk, for cleft lip: not yet rec'd. No other info.
Congenital disorders	2003GB01276 Serious	32 wk/ M/2.3 kg	400 mg/day; duration unk	Not provided	Magnesium	PTs: Retinal coloboma, Cardiac murmur. Baby born at 32 wks gestation w/ systolic murmur + coloboma of right eye w/ likely blindness. Baby not yet rec'd. No other info.
	2002GB02894 Serious	Age unk/ M/wt unk	400 mg/day; thru pregnancy until 3 days prior to delivery	Pre-eclamptic toxemia, asthma, depression, 1 prior pregnancy, non-smoker	Citalopram	PTs: Talipes Mother developed pregnancy induced HTN. Seroquel + citalopram d/c'd 3 days before induction of labor. Healthy baby born w/ slight bilateral talipes. Outcome unk. No other info.
Fetal distress syndrome	2003GB00420 Serious	37 wk s/F/4.1 kg	700 mg/day at time of conception; 300 mg/day for rest of pregnancy	Asthma, previously smoked cannabis, smoked during pregnancy (unspecified)	Fluoxetine, lorazepam, fluvoxamine (1st trimester then d/c'd)	PTs: Fetal distress syndrome, Nosocomial infection, Jaundice neonatal, Oedema. Mother had severe pre-eclampsia, hospitalized x 2 wks, induced labor at 37 wks gestation. Prolonged labor w/ fetal distress. Tx=emergency C-section. Baby born w/ edema, jaundice, breathing + feeding difficulties associated w/ hospital acquired infection. Tx: IV abx. Baby rec'd from all events on Day 7. No other info.

Table 6 Multiple reports for serious CDS unlisted topics (15 reports)

Topic	Report	Age/ Sex/ Wt	Dose/ Duration	Mother's medical History	Concomitant medications	PTs/Comments
Fetal distress syndrome	2004AP01045 Non-serious	7 wks/M /3.04 kg	800 mg/day x 2 wks, to 1200 mg/day at 34 wks gestation to end of pregnancy	Schizoaffective disorder, HTN starting at 37 wks gestation, valproate OD at 36 wks gestation	Sertraline, diazepam, oxprenalol @ 38 wks for HTN, sodium valproate OD @ 36 wks.	PTs: Fetal distress syndrome, Neonatal complications of substance abuse, Drug withdrawal syndrome neonatal, Jaundice neonatal, Weight ↓ neonatal 39 wks: labor induced. Emergency C-section d/t fetal distress. Oxygen for NB at birth. Baby had tremors, jittery, ↑ muscle tone, irritability, perineal rash, jaundice, lost 150 g over 5 days. Discharged home Day 7. Day 10 no signs of drug withdrawal. Rec'd from all events by 4 wks.

[a] for which premature delivery has been reported, [b] for which neonatal withdrawal has been reported, wk(s)=week(s), kg=kilograms, tx=treatment, EEG=electroencephalogram, US=ultrasound, WNL=within normal limits, d/t=due to, rec'd=recovered, rec'g=recovering, unk or ?=unknown, w/=with, NB=newborn, info=information, mo(s)=month(s), dx=diagnosis, y=year(s), UTI=urinary tract infection, VSD=ventricular septal defect, HTN=hypertension, C-section=caesarean section, IV=intravenous, abx=antibiotics, wt=weight

Summary for multiple reports for serious CDS unlisted topics

Premature baby: One report (1999AP06076) was confounded by a concomitant medication (fluoxetine) taken by the mother during the pregnancy, for which premature delivery has been reported. In addition, the mother had DM, which can contribute to early labor. Two other reports (2004UW17483, 2004UW17484) of premature baby involved two different pregnancies for the same mother. The mother was also taking sertraline during both pregnancies; therefore a causal relationship between the events and SEROQUEL could not be established. The fourth report (2004AP04599), which described a male neonate delivered prematurely at 35 weeks, was confounded by the mother's short cervix with early dilation which is a risk factor for prematurity. There were no reports that contained the MedDRA preferred term "Premature baby" at the secondary preferred term level.

Neonatal drug withdrawal: Two reports were confounded by concomitant medications taken by the mother, for which neonatal withdrawal has been reported (2002GB02909: diazepam, fluoxetine; 2001AP03788: diazepam, venlafaxine). One of these (2001AP03788) was also confounded by the mother's history of opiate and benzodiazepine dependence. The two remaining reports (2003AP03328; 2004UW03627) contained minimal information and thus provided inadequate information to attribute causality to SEROQUEL.

In addition, five other reports contained the MedDRA preferred term "Drug withdrawal syndrome neonatal" as a secondary preferred term. All five of these reports were confounded by concomitant medications taken by the mother during pregnancy, for which neonatal withdrawal has been reported (2003UW13923: paroxetine, 2002GB02278: paroxetine, 2001UW01690: paroxetine, 2004AP01045: diazepam, 2003SE05724: venlafaxine).

Congenital disorders: Approximately three percent of live born infants have a major congenital anomaly. About one half of these anomalies are detected at birth; the remainder become evident later in childhood or, less often, adulthood. Although non-genetic factors may cause malformations, genetic factors are usually responsible. Before day 31, exposure to a teratogen produces an all-or-none effect. With exposure around conception, the conceptus usually either does not survive or survives without anomalies. Because so few cells exist in the early stages, irreparable damage to some may be lethal to the entire organism. If the organism remains viable, however, organ-specific anomalies are not manifested, because either repair or replacement will occur to permit normal development. A similar insult at a later stage may produce organ-specific defects (Simpson 2002).

One report of congenital hypoventilation syndrome (2000AP01959) was confounded by a concomitant medication (citalopram) that they baby's mother was taking during pregnancy (duration unknown). Neonates exposed to citalopram late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings included respiratory distress, cyanosis, and apnea. These features are consistent with either a direct toxic effect of SSRIs and SNRIs, or possibly a drug discontinuation syndrome (Physician's Desk Reference; Celexa [citalopram]).

One report (2003GB00079) described a baby who was born with a ventricular septal defect (VSD). The mother discontinued therapy with SEROQUEL within the first month of pregnancy and received treatment with cephradine during the last three weeks of pregnancy. No other concomitant medications were reported and the mother had a history of two previous normal pregnancies. VSD is the most common form of congenital heart defect and accounts for 15% to 20% of all such defects (not including cyanotic congenital heart defects). Spontaneous closure occurs in 30% to 40% of patients with membranous VSDs and muscular VSDs during the first six months of life. Defects result from a deficiency of growth or a failure of alignment or fusion of component parts (Park 2002). The etiology of VSDs is unknown, however several known risk factors for VSD, including a family history of congenital heart disease and exposure to certain drugs, infectious agents, and maternal metabolic disturbances, explain few cases (Newman 1985).

One report (2003PK01557) described a baby who was born with a cleft lip. This mother began treatment with SEROQUEL during the 14th week of pregnancy (2nd trimester) and discontinued therapy with SEROQUEL during the 24th week of pregnancy. The mother then developed a varicella infection two weeks later. Possible causes include extrinsic factors (ie, maternal drug exposure [anticonvulsants, dextromorphan, etc] smoking), a syndrome-malformation complex, or genetic factors (Wyllie 2004). The latest time during embryonic development that cleft lip will occur is 36 days post conception (VanAllen and Hall 2000). Given that therapy with SEROQUEL was not started until the 14th week of pregnancy and the baby's mother smoked during pregnancy a causal relationship between cleft lip and SEROQUEL could not be established.

One report (2002GB02894) described a baby born with mild talipes. Talipes is generally the result of fetal crowding due to a decreased volume of amniotic fluid or breech presentation, which may trap the fetus' legs between their body and the uterine wall (Jones 2004). The last report (2003GB01276) contained limited information and therefore did not lend itself to analysis.

Fetal distress syndrome: One report was confounded by the mother's medical history (2003GB00420: cannabis smoking during the pregnancy and prior. The other report of fetal distress syndrome (2004AP01045) was confounded by the mother's concurrent hypertension and induction of labor.

Taken together, these reports were confounded or contained scant clinical detail and did not establish a causal relationship between premature baby, neonatal drug withdrawal, congenital disorders, and fetal distress syndrome and SEROQUEL trans-placental exposure.

Single reports for serious CDS unlisted topics

Single reports for serious CDS unlisted topics are contained in Table 7 below.

Table 7 Single reports for serious CDS unlisted topics (13 reports)

Topic	Report #/ Seriousness	Age/ Sex/Wt	Dose/ Duration	Mother's medical History	Concomitant medications	PTs/Comments
SOC: Cardiac disorders						
Cardiac disorders	2003SE05566[a] Serious	37 wk/ F/2.6 kg	600 mg/day; 3rd trimester only	Not provided	Not provided	PTs: Cardiac arrest, Abdominal distension, Enterocolitis, Compartment syndrome C-section for premature membrane rupture. Day 2 of life: baby developed intestinal distension, NEC, compartment syndrome and died on Day 7 d/t cardiac arrest. No other info.
SOC: Respiratory, thoracic, and mediastinal disorders						
Respiratory disorders	2002PK00498 Serious	Full-term/M/ 3.48 kg	400 mg/day x 1 mo; ↓ 200 mg x 9 mos	Psychotic disorder, sleep disorder, anemia	Zolpidem, folic acid	PTs: Neonatal respiratory failure, Convulsion neonatal, Hypotonia neonatal, C-section. NB w/ respiratory insufficiency requiring artificial ventilation, muscular hypotonia. Seizure on Day 5. Baby rec'd; date unk.
	2003UW11441 Serious	Age, Sex, Wt unk	Dose/ duration unk	Not provided	Not provided	PTs: Dyspnea, Tachycardia, Respiratory rate increased NB w/ trouble breathing, tachycardia, rapid breathing. Outcome unk.
SOC: Nervous system disorders						
Nervous system disorders	2003UW13923 Serious	Age, Sex, Wt unk	Dose/ duration unk	Not provided	Paroxetine[b], phenytoin	PTs: Agitation neonatal, Hypertonia, Irritability, Drug withdrawal syndrome neonatal. NB jittery, hypertonic, irritable, withdrawal sxs. Outcome unk.
	2001UW01690 Serious	Age unk/F/ 2.9 kg	100 mg/day; duration unk	Suicide attempt	Clonazepam, paroxetine	PTs: Hyperreflexia, Drug withdrawal syndrome neonatal, Hypoxia. Baby had hyperreflexia + hypoxia at birth. Tx: oxygen. Rec'd from all events.
	2003AP01530 Serious	Full-term/M/ 3 kg	25 mg/day; entire pregnancy	Anxiety disorder	Paroxetine[b]	PTs: Tremor neonatal. Baby had lower + upper limbs tremor. Day 6 of life: Seroquel blood level= <2.50 mg/mL. Baby recovering at time of report. No other info.
SOC: Gastrointestinal disorders						

Table 7 Single reports for serious CDS unlisted topics (13 reports)

Topic	Report #/ Seriousness	Age/ Sex/Wt	Dose/ Duration	Mother's medical History	Concomitant medications	PTs/Comments
GI symptoms	2004GB00629 Non-serious	2 wks overdue/ F/ 4.1 kg	400 mg/day; duration unk	Not provided	Not provided	PTs: Diarrhea, Muscle twitching, Tremor, Crying, Sedation, Sneezing, Feeding problem in child. 2 wks overdue: failed induction x2. C-section. Baby had diarrhea, muscle twitching, tremor, crying, sedation, sneezing, feeding problems. Outcome unk. No other info.
	2003GB00111 Serious	Full-term/M/ 2.9 kg	200 mg/day; entire pregnancy	1 abortion, 1 miscarriage, smoked 10-15 cigarettes/day	Not provided	PTs: Dysphagia. Mother had left sided weakness at 3 mos gestation. Sick neonate admitted to special baby care unit for 1 wk d/t swallowing difficulties. Mother later diagnosed w/ MS. Baby rec'd from dysphagia
SOC: General disorders and administration site conditions						
General disorders	2003GB01471 Serious	37 wks/ F/2.62 kg	600 mg/day; entire pregnancy	Two suicide attempts during pregnancy.	Lorazepam[c]	PTs: Pyrexia, Agitation neonatal, Feeding problem in newborn, Neonatal respiratory distress syndrome, Developmental delay. Elective C-section. 20 min after birth baby had respiratory distress syndrome. Tx=oxygen. 24 hrs: jittery, hypertonic, poor feeding, fever reported to be d/t drug withdrawal. Day 6 of life: tremor resolved. Day 11 of life: discharged to home. 4 mos: diagnosed w/ developmental delay and possible craniosynotosis. Rec'd from all events except developmental delay.
	2003SE05724 Serious	37 wks/ M/Wt unk	250 mg/day until wk 12, 25 mg/day rest of pregnancy	DM, depression, alcoholism, smoke 15 cigarettes/day	Venlafaxine[b], methyldopa, insulin, insulatard injection	PTs: Chills, Drug withdrawal syndrome neonatal, Hyperbilirubinemia, Psychomotor hyperactivity, Dyspnea. C-section d/t poor progression. Baby had motor agitation, quivering, fluttering, slight gasping of breath. Tx: CPAP. Day 4: Tx w/ phenobarbital d/t ↑ withdrawal sxs. Day 7: improved. Day 9: phenobarbital dose ↓. Day 20: phenobarbital d/c'd. Baby rec'd

Table 7 Single reports for serious CDS unlisted topics (13 reports)

Topic	Report #/ Seriousness	Age/ Sex/Wt	Dose/ Duration	Mother's medical History	Concomitant medications	PTs/Comments
General disorders	2002GB02278 Serious	37 wks/ F/2.55 kg	800 mg/day; entire pregnancy	Non-smoker, no alcohol use, no substance abuse, no significant family history	Paroxetine[b], pethidine	PTs: Neonatal disorder, Hypotonia neonatal, Drug withdrawal syndrome neonatal, Hypervigilance, Feeding problem in newborn, Insomnia. At birth baby inhaled meconium + was hypotonic, hypervigilant. Over next 24 hrs: "twitchier than normal" + "jittery baby." Day 3 of life: hypotonic, hypervigilant, unable to feed without inhaling. Tx=tube feedings. Day 9 of life: Baby rec'd + discharged to home
SOC: Skin and subcutaneous tissue disorders						
Eczema	2004UW07087 Non-serious	Age, sex, wt unk	Dose/ duration unk	Not provided	Not provided	PTs: Eczema. Baby born healthy. At 6 mos of age: eczema. Outcome unk. No other info.
Miscellaneous events						
Miscellaneous	2003GB03136 Serious	Full-term/M/ 2.5 kg	600 mg/day; first 4 weeks of pregnancy only	Smoker, cannabis, alcohol use/ amphetamine use, abortion, vaginal bleed d/t self-harm	Chlorpromazine, folic acid	PTs: Umbilical cord around neck, Renal disorder. C-section d/t umbilical cord around neck. At birth one kidney not functioning d/t fluid build-up. Later resolved. No other info.

[a] see section 6.1 Reports with an outcome of death, [b] for which neonatal withdrawal has been reported, [c] for which drug withdrawal has been reported, wt=weight, C-section=caesarean section, NEC= necrotizing enterocolitis, d/t=due to, info=information, mo(s)=month(s), NB=newborn, w/=with, rec'd=recovered, unk=unknown, sxs=symptoms, tx=treatment, wks=weeks, MS=multiple sclerosis, min=minutes, hr(s)=hour(s), CPAP=continuous positive airway pressure.

Summary for single reports for serious CDS unlisted topics

Cardiac disorders: This report (2003SE05566; "Cardiac arrest") described a baby who was born at 37 weeks gestation and was delivered without problems. However on Day 2, the baby developed intestinal distention, necrotizing enterocolitis, and compartment syndrome and died one week later of cardiac arrest. See section 6.1 *Topics of interest; Reports with an outcome of death* for more details.

Respiratory, thoracic, and mediastinal disorders: One report (2002PK00498; "Neonatal respiratory failure") described a baby who experienced respiratory insufficiency and muscular hypertonia at birth, and a seizure on day five of life. The baby recovered and further development was reported to be normal. This baby's mother received SEROQUEL throughout her entire pregnancy and zolpidem for the first seven months of the pregnancy. The other report (2003UW11441: "Dyspnea") contained scant clinical detail and did not lend itself to analysis. In addition, on report contained the MedDRA preferred term "Dyspnoea" as a secondary term. This report (2003SE05724) was confounded by the mother's history of smoking 15 cigarettes/day during pregnancy and by a concomitant medication (venlafaxine) for which neonatal withdrawal has been reported.

Nervous system disorders: One report (2003UW13923; "Agitation neonatal") was confounded by a concomitant medication (paroxetine) for which drug withdrawal has been reported. In addition, two other reports contained the MedDRA preferred term "Agitation neonatal" as a secondary preferred term. One of these (2003GB01471) was confounded by a concomitant medication (lorazepam) for which drug withdrawal has been reported and the other report (2003AP03328) contained scant clinical detail and did not lend itself to analysis.

Hyperreflexia: One report (2001UW01690; "Hyperreflexia") was confounded by a concomitant medication (paroxetine) for which neonatal withdrawal has been reported.

Tremor: One report (2003AP01530: "Tremor") was confounded by a concomitant medication (paroxetine) for which neonatal withdrawal has been reported. In addition, one other report contained the MedDRA preferred term "Tremor" as a secondary preferred term. This report (2004UW03627) contained scant clinical detail and did not lend itself to analysis.

Gastrointestinal disorders: One report (2004GB00629; "Diarrhea") contained scant clinical detail and did not lend itself to analysis. One report (2003GB00111; "Dysphagia") was confounded by the mother's history of smoking during her entire pregnancy. Additionally, this mother was diagnosed with multiple sclerosis after delivery.

General disorders and administration site conditions: One report (2003GB01471; "Pyrexia") contained limited information about the baby's fever and so a causal relationship could not be determined. One report (2003SE05724; "Chills") described a baby experiencing drug withdrawal. This baby's mother had taken venlafaxine (for which neonatal withdrawal has been reported) during her pregnancy. One report (2002GB02278; "Neonatal disorder") described a baby who inhaled meconium during delivery. The baby recovered by day 9 of life. In addition, two other reports contained the MedDRA preferred term "Neonatal disorder"

as a secondary term. One of these two reports (2004AP04599) described neonatal obstinence syndrome and the other (2000AP01959) described an unspecified eye abnormality. Both of these reports contained scant clinical detail about the event (neonatal obstinence syndrome and eye abnormality) and did not lend themselves to analysis.

Skin and subcutaneous tissue disorders: One report (2004UW07087: "Eczema") contained scant clinical detail and did not lend itself to analysis.

Miscellaneous reports: One report (2003GB03136; "Umbilical cored around neck") described a baby who was born with the umbilical wrapped around his neck. The baby recovered without sequelae.

Following a review of the data, it was determined that the data do not establish a causal relationship between the topics reviewed in this table and the use of SEROQUEL in pediatric patients.

Multiple reports for non-serious CDS unlisted topics

Multiple reports for non-serious CDS unlisted topics are listed in Table 8 below.

Table 8 Multiple reports for non-serious topic (2 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Normal newborn	2001AP00607	Normal newborn	No	None	NA
	1999UW02483	Normal newborn	No	None	NA

Summary for multiple reports for non-serious CDS unlisted topics

Of the two reports of normal newborns, one report (2001AP00607) described a mother who received SEROQUEL (500 mg/day) and venlafaxine, diazepam, zopiclone and ferrous sulfate as concomitant medication. A healthy baby was born. Another report (1999UW02483) contained minimal information concerning a healthy baby born while the mother received SEROQUEL. In addition, one other report contained the MedDRA preferred term "Normal newborn" as a secondary preferred term. This report (2001AP03788) described a baby who experienced mild drug withdrawal symptoms and recovered within one week. No other information was provided.

Single reports for non-serious CDS unlisted topics

There were no single reports for non-serious CDS unlisted topics received.

5.4.2 Infants and toddlers (age 28 days to 23 months; 2 reports)

5.4.2.1 CDS listed topics (0 reports)

There were no reports for this age group that contained a primary preferred term, which referred to a topic that is listed in the SEROQUEL CDS.

5.4.2.2 CDS unlisted topics (2 reports)

Multiple reports for serious CDS unlisted topics

Multiple reports for serious CDS unlisted topics are contained in Table 9 below.

Table 9 Multiple reports for serious CDS unlisted topics (2 reports)

Topic	Report	Age/ sex	Dose/ TTO	Medical History	Concomitant medication	PTs/Comment
Accidental exposure	1998UW48084 Serious	12 mo/ F	200 mg/ day	Not provided	Not provided	PTs: Accidental exposure, Coma, Leukocytosis. Child accidentally ingested Seroquel; went into coma. Rec'd. Now has leukocytosis. WBC = 22,000/mm^3; neutrophils = 15%. Leucocytosis not rec'd.
	1998UW49889 Serious	20 mo/ F	100 mg/ day	Not provided	Not provided	PTs: Accidental exposure, Heart rate increased. Child accidentally ingested Seroquel; had ↑ pulse (100 to 130 bpm). Tx.=90 cc charcoal. Pt rec'd.

mo=month, rec'd=recovered, WBC=white blood cell, bpm=beats per minute, tx=treatment

Summary for multiple reports for serious CDS unlisted topics

Two reports containing the MedDRA preferred term of "Accidental exposure" were received. The first report (1998UW49889) described a 20-month-old female child who accidentally ingested a 100 mg tablet of SEROQUEL and experienced an increased pulse rate. The patient was treated with 90 cc of charcoal and recovered. The other report (1998UW48084) described a 12-month-old female who accidentally ingested 200 mg of SEROQUEL and went into a coma. She recovered from the coma, but developed leukocytosis (however, her cardiovascular system was stable). The leukocytosis had not resolved by three days after the accidental ingestion. Information on baseline blood levels, medical history, or concomitant medications were not provided.

Tachycardia and coma are listed events in the SEROQUEL CDS. Following a review of these reports, it was determined that the data was insufficient to establish any new significant safety issues regarding the use of SEROQUEL in children.

Reports for non-serious CDS unlisted topics

There were no reports for the non-serious CDS unlisted, topics section.

5.4.3 Children (age 2 to 11 years; 199 reports)

5.4.3.1 CDS listed topics (77 reports)

Multiple reports for CDS listed topics

The reports associated with CDS listed (serious and non-serious) topics for which multiple reports were received, are contained in Table 10 below.

Table 10 Multiple reports for CDS listed topics (74 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Blood and lymphatic system disorders					
Blood disorders	2002UW09817	Granulocytopenia	Yes	Leukopenia	Yes
	2004UW07848	Neutrophil count ↓	Yes	WBC count ↓	Yes
	2004UW04214	Neutrophil count ↓	Yes	WBC count ↓ Abdominal pain upper	Yes No
	2002UW04998	Neutrophil count ↓	Yes	None	NA
	2000UW05002	Neutropenia	No	None	NA
	2004UW03955	Neutropenia	No	None	NA
	2004UW17067	Neutropenia	No	None	NA
	2002UW05374	Leukopenia	No	Neutropenia	No
SOC: Cardiac disorders					
Tachycardia	2001UW06526	Tachycardia	No	None	NA
	2002AP02680	Sinus tachycardia	No	Chest pain Dyspnoea exertional	No No
	2004UW12859	Heart rate ↑	No	None	NA
SOC: Injury, poisoning, and procedural complications					
Overdose[a]	1995AP08538	Overdose	Yes	Sedation	Yes
	2000UW03156	Overdose	Yes	Respiratory distress Convulsion Lethargy	Yes Yes No
	2002AP02020	Overdose	Yes	Agitation Somnolence	Yes Yes
	2004AC00397[c]	Intentional overdose	Yes	Intentional misuse Injury asphyxiation	Yes Yes
SOC: Investigations					
Hepatic disorders	1998UW49829	LFT abnormal (ALT, GGT, AST)	Yes	None	NA
	2002UW10098	Hepatic enzyme ↑	No	None	NA
	2003UW01959	Hepatic enzyme ↑	No	None	NA
Increased weight[d]	2001UW02582	Weight ↑	No	None	NA
	2001UW10154	Weight ↑	No	None	NA
	2001UW10901	Weight ↑	No	None	NA
	2002UW03308	Weight ↑	No	None	NA
	2004UW07409	Weight ↑	No	None	NA
	2004UW07567	Weight ↑	No	None	NA

Table 10 Multiple reports for CDS listed topics (74 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Increased weight[d]	2004UW15668	Weight ↑	No	None	NA
SOC: Nervous system disorders					
Convulsion	1999AP05419	Convulsion	Yes	None	NA
	2003UW09378	Convulsion	Yes	None	NA
	2004UW12243	Convulsion	Yes	None	NA
	2003UW05886	Convulsion	No	None	NA
Extrapyramidal symptoms[e]	2003AP04288	Extrapyramidal disorder	Yes	None	NA
	2004UW02295	Extrapyramidal disorder	No	None	NA
	2004UW12966	Extrapyramidal disorder	No	None	NA
	2004UW15270	Extrapyramidal disorder	No	None	NA
	2003UW04443	Movement disorder	Yes	None	NA
	2002UW06808	Dystonia	Yes	None	NA
	2001UW00177	Dystonia	No	None	NA
	2002UW14926	Dystonia	No	None	NA
	2002UW14868	Dystonia	No	None	NA
	2004UW06193	Akathisia	No	None	NA
	2002UW12947	Akathisia	Yes	Dystonia Dyskinesia	Yes Yes
	2003UW06318	Muscle twitching	Yes	Dyspnoea	Yes
	2002UW16351[b]	Muscle twitching	No	Agitation Flushing	No No
	2002UW12659	Dyskinesia	Yes	None	NA
	2003UW01918	Dyskinesia	Yes	None	NA
	1999UW03177	Dyskinesia	Yes	None	NA
	2001UW12258	Dyskinesia	No	Strabismus	No
	1998UW49956	Dyskinesia	No	None	NA
	1999UW01944	Dyskinesia	No	None	NA
	1999UW02175	Dyskinesia	No	None	NA
	2002UW06262	Tic (r/t EPS)	No	Extrapyramidal disorder	No
	2002UW14894	Tic (r/t EPS)	No	Extrapyramidal disorder	No
	2004UW12776	Torticollis	No	None	NA

Table 10 Multiple reports for CDS listed topics (74 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Extrapyramidal symptoms[e]	2003UW12446	Restlessness	No	Logorrheoea	No
	2003UW14889	Choreoathetosis	No	None	NA
Somnolence	2004UW02969	Somnolence	No	None	NA
	2001UW00775	Somnolence	No	Vision blurred Gait abnormal	No No
	2001AP02839	Somnolence	No	↓appetite Weight ↓	No No
	2001AP02836	Somnolence	No	↓appetite Weight ↓	No No
	2001UW16461	Sedation	No	None	NA
Syncope	2004SE05351	Syncope	Yes	None	NA
	2003UW05413	Syncope	No	None	NA
Tardive dyskinesia[f]	2001UW15005	Tardive dyskinesia	Yes	None	NA
	2002UW13474	Tardive dyskinesia	Yes	None	NA
	2002UW16191	Tardive dyskinesia	Yes	None	NA
	2002UW16921	Tardive dyskinesia	Yes	None	NA
	2003UW06087	Tardive dyskinesia	Yes	None	NA
	2003UW07033	Tardive dyskinesia	Yes	None	NA
	2003UW09443	Tardive dyskinesia	Yes	None	NA
	2004UW09544	Tardive dyskinesia	Yes	None	NA
	1999UW00525	Tardive dyskinesia	No	Eye rolling Dyskinesia	No No
	2001UW01237	Tardive dyskinesia	No	None	NA
SOC: Reproductive system and breast disorders					
Priapism	2000UW03120	Priapism	Yes	None	NA
	2003UW16450	Priapism	No	None	NA
	2003UW09992	Erection ↑	No	None	NA

[a,b,c,d,e,f] see section 6.14, 6.13, 6.1, 6.5, 6.8, and 6.7 respectively (*Special topics of interest*) for a discussion of these reports, WBC=white blood cell, ALT=alanine transaminase, AST=aspartate transaminase, GGT=gamma-glutamyl transferase, r/t=related to, EPS=extrapyramidal syndrome, LFT=liver function tests, ↑=increased, ↓decreased.

In addition to the reports listed in the table above, some reports were received that contained events reported at the secondary preferred term level (not the first event reported) for the topics covered in this table. The reports which had an event listed as a secondary preferred term include the following: "Convulsion" (2000UW03156), "Akathisia" (1999AP05604),

"Dystonia" (2001UW11878, 2003UW06962, 2001UW12261, 2002UW12947, 2000UW04018), "Dyskinesia" (2003UW16639, 1999UW00525, 2002UW12947, 2001UW12073), "Extrapyramidal disorder" (2002UW06262, 2002UW14894), "Muscle twitching" (2001UW07141, 2001UW11878), "Tremor" (2003UW16639, 1999U04138, 2001UW12073), "Hepatic enzyme increased" (2000UW03202), "Liver function test abnormal" (2004UW10733), "Neutropenia" (2002UW05374), "Leukopenia" (2001UW12259, 202UW09817), "White blood cell count decreased" (2004UW07848, 2004UW04214, 2003UW09289), "Weight increased" (2004UW10733, 2002UW12495, 2004UW19620, 1999AP05794, 1999AP05734), "Tachycardia" (2004UW17710), "Sinus tachycardia" (2001UW12073), "Somnolence" (2002AP02020), "Sedation" (1995AP08538), "Psychomotor hyperactivity" (2001UW10765), and "Lethargy" (2000UW03156).

Summary for multiple reports for CDS listed topics

The AEs contained in Table 10 as well as in the paragraph above are listed in the SEROQUEL CDS for the adult population. Following a review of all these reports, it was determined that there was no difference in frequency, severity or characteristics of these events when compared to the known safety profile of SEROQUEL in adults.

Single reports for CDS listed topics

Reports associated with CDS listed topics, for which only a single report was received, are contained in Table 11 below.

Table 11 Single report for CDS listed topic (3 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: General disorders and administration site conditions					
Edema	2004UW19532	Oedema peripheral	No	None	NA
SOC: Metabolism and nutrition disorders					
Lipids	2004UW10733	Hypercholesterolaemia	No	Blood triglycerides ↑ LFT abnormal Weight ↑	No No No
SOC: Skin and subcutaneous tissue disorders					
Urticaria	2003UW09379	Urticaria	No	None	NA

↑=increased, LFT=liver function test.

In addition to the reports listed in the table above, two reports were received that contained events reported at the secondary preferred term level (not the first event reported) for the topics covered in this table. These reports contained either the MedDRA preferred term "Lipids increased" (2004UW08948) or "Blood triglycerides increased" (2004UW10733) as secondary terms.

Summary for single reports for CDS listed topics

Following a review of these reports, it was determined that there was no difference in frequency, severity or characteristics of these events when compared to the known profile of SEROQUEL in adults.

5.4.3.2 CDS unlisted topics (122 reports)

Multiple reports for serious CDS unlisted topics

Multiple reports for serious CDS unlisted topics are contained in Table 12 below. In addition, narratives for these reports are contained in Appendix B.

Table 12 Multiple reports for serious topic (14 reports)

Topic	Report #/ Seriousness	Age/ Sex	Dose/TTO	Medical History	Concomitant medications	PTs/Comment
SOC: Cardiac disorders						
QT prolongation	2003UW01101 Non-serious	-	-	-	-	PTs: Electrocardiogram QT prolonged See section 6.6 *Prolonged QT*
	2003UW09322 Non-serious	-	-	-	-	PTs: Electrocardiogram QT prolonged See section 6.6 *Prolonged QT*
SOC: Eye disorders						
Cataract	2000UW01591 Serious	-	-	-	-	PTs: Cataract, Visual acuity reduced See section 6.9 *Cataract*
	2002UW12495[a] Non-serious	-	-	-	-	PTs: Cataract, Weight increased See section 6.9 *Cataract*
	2001UW01918 Non-serious	-	-	-	-	PTs: Vision blurred See section 6.9 *Cataract*
SOC: Metabolism and nutrition disorders						
Glucose dysregulation	2003UW03648 Non-serious	-	-	-	-	PTs: Diabetes mellitus See section 6.2 *Glucose dysregulation*
	2004AP00095 Serious	-	-	-	-	PTs: Diabetes mellitus See section 6.2 *Glucose dysregulation*
	2004AP03990 Serious	-	-	-	-	PTs: Diabetes mellitus insulin-dependent See section 6.2 *Glucose dysregulation*
	2001UW00363 Serious	-	-	-	-	PTs: Diabetes mellitus insulin-dependent See section 6.2 *Glucose dysregulation*
	2004UW17777 Non-serious	-	-	-	-	PTs: Blood glucose increased See section 6.2 *Glucose dysregulation*
	2004UW06024 Non-serious	-	-	-	-	PTs: Blood glucose increased See section 6.2 *Glucose dysregulation*

Table 12 Multiple reports for serious topic (14 reports)

Topic	Report #/ Seriousness	Age/ Sex	Dose/TTO	Medical History	Concomitant medications	PTs/Comment
Glucose dysregulation	2004UW08948 Serious	-	-	-	-	PTs: Hypoglycaemia, Hyperglycaemia, Lipids increased See section 6.2 *Glucose dysregulation*
SOC: Nervous system disorders						
Speech disorder	2002SE04289 Serious	Child /M	25 mg/day; one day	Autism, asthma, behavior problems	Not provided	PTs: Speech disorder, Incontinence, Pallor, Cyanosis, Dizziness postural, Fatigue 20 minutes after 1st dose Pt had incontinence, exhaustion, speech disorder, dizziness, pallor. Seroquel D/c'd. Pt fell asleep, woke up next day feeling well. No other info.
	2001UW12073[b] Serious	-	-	-	-	PTs: Speech disorder, Body temperature increased, Tremor, Wheezing, Blood urea increased, Confusional state, Dyskinesia, Depressed level of consciousness, Cough, Blood creatinine phosphokinase increased, Hyperhidrosis, Fall, Gait abnormal, Blood lactate dehydrogenase, Muscle rigidity, Restlessness, Sinus tachycardia, Flushing, Death. See section 6.1 *Reports with an outcome of death.*

[a,b] these reports are also cross-referenced in sections 6.5 and 6.8, respectively, D/c'd=discontinued, info=information, TD=Tardive dyskinesia.

Summary for multiple reports for serious CDS unlisted topics

For an analysis of the reports of glucose dysregulation, cataracts, and QT prolongation see Topics of Interest sections 6.2, 6.9, and 6.6, respectively.

Of the two serious reports of "Speech disorder," one (2001UW12073) had an outcome of death and is discussed in Topics of interest section 6.1 Reports with an outcome of death. The second report (2002SE04289) contained no information about concomitant medications, in addition to being confounded by the patient's current medical condition (autism); therefore assessment of causality was difficult.

Multiple reports for non-serious CDS unlisted topics

The reports associated with multiple reports for non-serious CDS unlisted topics are contained in Table 13 below.

Table 13 Multiple reports for non-serious topics (72 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Blood and lymphatic system disorders					
Bleeding disorders	2002UW03957	Prothrombin level ↑	No	None	NA
	2003UW09824	Ecchymosis	No	None	NA
	2003UW05623	Epistaxis	No	None	NA
	2003UW09741	Gingival bleeding	No	None	NA
SOC: Eye disorders					
Eye disorders	1998UW49818	Vision blurred	No	None	NA
	2002UW12468	Vision blurred	No	None	NA
	2004UW19936	Vision blurred	No	None	NA
	2004UW04018	Visual disturbance	No	None	NA
	2003UW00421	Eye rolling	No	None	NA
	2002UW04029	Eyelid disorder	No	None	NA
	2002UW16200	Mydriasis	No	None	NA
	2003UW12066	Oculogyration	Yes	None	NA
SOC: General disorders and administration site conditions					
Abnormal gait	2004UW17782	Difficulty walking	No	None	NA
	2003UW16639[a]	Gait abnormal	No	Tremor Dyskinesia Dysarthria	No No No
Drug interaction	1999UW04138[a]	Drug interaction	No	Tremor	No
	2000UW04117	Drug interaction	No	Drug level ↑	No

Table 13 Multiple reports for non-serious topics (72 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Drug interaction	2003UW09289	Drug interaction	No	WBC count ↓	No
Lack of effect	1999UW03728	Drug ineffective	No	None	NA
	2001UW11878	Drug ineffective	No	Dystonia Muscle twitching	No No
	2003UW06365	Drug ineffective	No	None	NA
	2003UW11482	Drug ineffective	No	None	NA
	2002UW00520	Therapeutic response ↓	No	None	NA
Pyrexia	2004UW09960	Pyrexia	No	None	NA
	2004UW13716	Pyrexia	No	None	NA
SOC: Investigations					
Ammonia ↑	2000UW03202	Ammonia ↑	No	Hepatic enzyme ↑	No
	2002UW12780	Ammonia ↑	No	None	NA
Weight decreased	2002UW01335	Weight ↓	No	Anorexia Vomiting	No No
	2001UW11378[b]	Weight ↓	No	Gynaecomastia	No
SOC: Metabolism and nutrition disorders					
Increased appetite	2004UW19620[c]	↑ appetite	No	Weight ↑ Abdominal distention Swelling face Dysuria	No No No No
	1999AP05794[c]	↑ appetite	No	Weight ↑	No
	1999AP05734[c]	↑appetite	No	Weight ↑	No
SOC: Nervous system disorders					
Tic	2003UW03682	Tic	No	None	NA
	2002UW15151	Motor dysfunction (verbatim=motor ticks)	No	None	NA
SOC: Psychiatric disorders					
Anxiety	2001UW16102	Anxiety	No	Blood pressure ↑ Arthralgia	No No
	2002UW03232	Anxiety	No	Hallucination, auditory	No
	2004UW06218	Panic attack	No	None	NA
Behavioral disturbances[d]	1998UW43327	Aggression	No	Drug interaction	No
	2000UW04125	Aggression	No	Hostility	No

Table 13 Multiple reports for non-serious topics (72 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Behavioral disturbances[d]	2001UW03757	Aggression	No	None	NA
	2001UW10765	Aggression	No	Psychomotor hyperactivity Hostility	No No
	2001UW01740	Aggression	No	None	NA
	2001UW01808	Aggression	No	None	NA
	2004UW15815	Aggression	No	Agitation	No
	2004UW01647	Agitation	No	Discomfort Urinary incontinence	No No
	2001AP00341	Agitation	No	None	NA
	2001UW04812	Agitation	No	Aggression Disinhibition	No No
	2001UW07141[a]	Agitation	No	Depressed mood Muscle twitching	No No
	2002GB02905	Agitation	No	Anxiety	No
	2004UW18888	Anger	No	None	NA
	1999AP05604[a]	Irritability	No	Abnormal behaviour Akathisia	No No
Flat affect	2003UW10203	Flat affect	No	None	NA
	2003UW10206	Flat affect	No	None	NA
Mania	2001UW02481	Mania	No	None	NA
	2001UW07079	Mania	No	None	NA
	2001UW07081	Mania	No	None	NA
	2001UW13781	Mania	No	None	NA
	2002UW15392	Mania	No	None	NA
	2003UW13879	Mania	Yes	None	NA
	2004UW07705	Mania	No	None	NA
SOC: Reproductive system and breast disorders					
Prolactin related disorders[b]	2003UW03532	Galactorrhoea	No	None	NA
	2003UW06694	Hair growth abnormal	No	None	NA
SOC: Respiratory, thoracic, and mediastinal disorders					
Throat disorder	2001UW12261[a]	Laryngospasm	Yes	Dystonia	Yes
	2004UW02125	Laryngitis	No	Hoarseness	No
	2004UW05347	Oesophageal disorder	No	None	NA

Table 13 Multiple reports for non-serious topics (72 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Skin and subcutaneous tissue disorders					
Skin disorders	2004UW12601	Rash	No	None	NA
	1998UW49936	Rash	No	None	NA
	2001UW05539	Rash	No	Headache Vision blurred	No No
	2003SE02607	Rash	Yes	Pyrexia	Yes
	2001UW09856	Photosensitive rash	No	None	NA
	1998UW46682	Acne	No	Rash maculo-papular Dermatitis exfoliative	No No
	2003UW02293	Dry skin	No	None	NA
	2003UW08741	Skin discolouration	No	Hyperhidrosis Pollakiuria	No No

[a,b,c,d] see sections 6.8, 6.11, 6.5, and 6.13, respectively a discussion of these reports. WBC=white blood cell count,↑=increased.

Summary for multiple reports for non-serious CDS unlisted topics

Bleeding disorders (4 reports): The report of increased prothrombin level (2002UW03957) was reported by the physician to be possibly due to the upward titration of lithium. The other three reports (2003UW09741: "Gingival bleeding," 2003UW09824: "Ecchymosis," 2003UW05623: "Epistaxis") contained scant clinical detail and did not lend themselves to analysis. No other reports contained MedDRA preferred terms describing bleeding disorders as secondary terms.

Eye disorders: One report (2003UW12066: "Oculogyration") contained incomplete information. The sequence of events in this report was unclear and no medical history was provided. The remaining seven reports (2004UW19936, 1998UW49818, 2002UW12468, 2004UW04018, 2003UW00421, 2002UW04029, 2002UW16200) contained scant clinical detail and did not lend themselves to analysis.

Four other reports contained MedDRA preferred terms describing eye disorders as secondary terms. One report (1999UW00525) of eye rolling was described to be a symptom of the patient's concurrent TD. One report (20001UW12258) of strabismus contained scant clinical detail but it was noted that the patient was concurrently receiving risperidone for which accommodation disturbances have been reported. Two reports contained the MedDRA preferred term "Vision blurred." One of these reports (2001UW5539) was confounded by a concomitant medication (bupropion) for which blurred vision has been reported and the other report (2001UW00775) contained scant clinical detail and did not lend itself to analysis.

Abnormal gait: One report (2003UW16639: "Gait abnormal") was confounded by a medication (fluoxetine) for which psychomotor impairment has been reported. The other report (2004UW17782: "Difficulty walking") contained scant clinical detail and did not lend itself to analysis.

Two other reports contained the MedDRA preferred term "Gait abnormal" as a secondary term. One report (2001UW12073) is discussed in section 6.1 *Topics of interest; Reports with an outcome of death*. The other report (2001UW00775) contained scant clinical detail and did not lend itself to analysis.

Drug interactions: One report (1999UW04138) described a patient who experienced tremors, which were considered by the physician to be due to an interaction between SEROQUEL and liothyronine. Tremors are listed in the SEROQUEL CDS, therefore the tremors could have occurred without a drug interaction. The next report (2003UW09289) described a patient who experienced a low white blood cell count. The physician suspected a drug interaction between SEROQUEL and valproate. Leukopenia is listed in the SEROQUEL CDS and has been reported with valproate use; thus, the event was likely due to either drug alone, rather than due to an interaction. The next report (2000UW04117) described a patient who experienced an increased blood valproate level. It was reported that the "patient's blood valproate level increased and decreased as the dose of valproate was increased and decreased." Therefore, the data does not suggest a drug interaction.

The SEROQUEL CDS states:

> "The pharmacokinetics of sodium valproate and SEROQUEL were not altered to a clinically relevant extent when co-administered."

An additional report contained the MedDRA preferred term "Drug interaction" as a secondary term. This report (1998UW43327) described a patient whose mother thought the patient was experiencing a drug interaction between SEROQUEL and methylphenidate. The physician thought that the patient's mood swings were an underlying problem of the patient's psychiatric illness and that the event was not related to a drug interaction or to SEROQUEL.

Lack of effect: Four of the patients, for whom a lack of effect was reported, were being treated for diseases other than schizophrenia or acute manic episodes in bipolar disorder (2001UW11878, 1999UW03728: ADHD, 2003UW06365: OCD, 2003UW11482: PTSD). The last report (2002UW00520: decreased therapeutic response) was received from a physician who reported that he "needs to push the doses higher to gain results." No other information was provided.

One other report contained the MedDRA preferred term "Drug ineffective" as a secondary term. This report (2004UW14830) described a patient who had been taking SERQOUEL for a year when he suddenly experienced anxiety, suicide attempt, depression, mood swings, anger, and obsessive thoughts after taking SEROQUEL from a new refill for. The patient was given a new lot of SEROQUEL and the events resolved.

Pyrexia: Both reports of pyrexia (2004UW09960, 2004UW13716) contained scant clinical detail and did not lend themselves to analysis.

Two other reports contained the following MedDRA preferred terms, "Pyrexia" (2003SE02607) and "Body temperature increased" (2001UW12073), as a secondary term. One report (2001UW12073) is discussed in section 6.1 *Topics of interest; Reports with an outcome of death*. The other report (2003SE02607) contained scant clinical detail and did not lend itself to analysis.

Ammonia increased: Both reports of increased ammonia (2000UW03202, 2002UW12780) contained scant clinical detail and did not lend themselves to analysis. No other reports contained MedDRA preferred terms describing ammonia disorders as secondary terms.

Weight decreased: One report (2002UW01335) described a patient who experienced decreased appetite, vomiting, and weight loss. The patient was treated with antacids, SEROQUEL continued, and the events abated. The other report (2001UW11378) described a patient who lost the weight he had gained while on olanzapine.

Two other reports, (2001AP02836, 2001AP02839) which contained the MedDRA preferred term "Weight decreased" as a secondary term, described patients who had experienced significant weight gain on other unspecified antipsychotics and then weight loss after starting SEROQUEL.

Increased appetite: One report (2004UW19620) was confounded by a concomitant medication (risperidone) for which increased appetite has been reported. The other two reports (1999AP05794, 1999AP05734) contained scant clinical detail and did not lend themselves to analysis. No other reports contained MedDRA preferred terms describing increased appetite as secondary terms.

Tics: One report (2003UW03682) contained scant clinical detail and did not lend itself to analysis. The other report (2002UW15151) was confounded by a concomitant medication (dextroamphetamine) for which tics have been reported. No other reports contained MedDRA preferred terms describing tics as secondary terms.

Anxiety: One report (2001UW16102) was confounded by a concomitant medication (bupropion) for which anxiety has been reported, one report (2002UW03232) was confounded by the patient's history of anxiety, and the third report (2004UW06218) contained scant clinical detail and did not lend itself to analysis.

Two other reports contained the MedDRA preferred term "Anxiety" as a secondary term. One report (2004UW14830) described a patient who had taken SEROQUEL for one year and suddenly experienced anxiety after taking SEROQUEL from a new refill for three days. The patient was given a new lot of SEROQUEL and the event resolved. The other report (2002GB02905) contained scant clinical detail and did not lend itself to analysis.

Behavioural disturbances: These reports will be discussed in section 6.13 *Topics of interest; Behavioral disturbances.*

Flat affect: Both reports (2003UW10203, 2003UW10206) contained scant clinical detail and did not lend themselves to analysis. No other reports contained MedDRA preferred terms describing flat affect as secondary terms.

Mania: The seven reports of mania (2001UW02481, 2001UW07079, 2001UW07081, 2001UW13781, 2002UW15392, 2003UW13879, 2004UW07705) contained scant clinical detail and did not lend themselves to analysis. No other reports contained MedDRA preferred terms describing mania as secondary terms.

Prolactin related disorders: These reports will be discussed in section 6.11 *Topics of interest; Hyperprolactinemia and associated adverse events.*

Throat disorders: One report (2001UW12261) described a patient who experienced laryngospasms related to dystonia. Olanzapine was discontinued and the patient recovered. Dystonia is listed in the SEROQUEL CDS and has also been reported for olanzapine. The other two reports (2004UW02125: "Laryngitis," 2004UW05347: "Esophageal disorder") contained scant clinical detail and did not lend themselves to analysis.

Skin disorders: Three reports were confounded by concomitant medications for which the event described has been reported (2004UW12601, 2001UW05539: "Rash" [valproate: rash], 2003UW08741: "Skin discoloration" [valproate: photosensitivity]). The remaining five reports contained scant clinical detail and did not lend themselves to analysis (2003UW02293, 1998UW46682, 1998UW49936, 2003SE02607, 2001UW09856).

Two other reports contained two MedDRA preferred terms each as secondary terms that described skin disorders. Both reports contained scant clinical detail and did not lend themselves to analysis (1998UW46682: "Dermatitis exfoliative," "Rash maculo-papular," 2003UW00170: "Eczema," "Psoriasis").

Single report for serious and non-serious CDS unlisted topics

Reports (both serious and non-serious) for CDS unlisted topics, for which only a single report has been received, are contained in Table 14 below.

Table 14 Single report for serious or non-serious CDS unlisted topic (36 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Ear and labryinth disorder					
Ear pain	2002UW15184	Ear pain	No	None	NA
Tinnitus	2003UW06698	Tinnitus	No	None	NA
SOC: Infections and infestations					
Pneumonia	2003UW02911	Pneumonia	Yes	None	NA

Table 14 Single report for serious or non-serious CDS unlisted topic (36 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Septic shock	2003UW04950	Septic shock	Yes	Blood test abnormal	Yes
SOC: Injury, poisoning, and procedural complications					
Accidental exposure	2000UW04018[a]	Accidental exposure	No	Dystonia	No
SOC: Musculoskeletal and connective tissue disorder					
Arthropathy	1999UW00265	Arthropathy	No	Muscular weakness	No
Rhabdomyolysis	2001UW12260	Rhabdomyolysis	Yes	None	NA
SOC: Nervous system disorders					
CNS function test abnormal	1999UW04393	CNS function test abnormal	No	None	NA
EEG abnormal	2004UW12248	EEG abnormal	No	None	NA
Headache	2001UW11805	Headache	No	None	NA
Loss of consciousness	2001UW01554	Loss of consciousness	Yes	Stupor Confusional state Urinary retention Nausea Headache	Yes Yes No No No
Paraesthesia	2003UW06962[a]	Paraesthesia	No	Dystonia Rhinitis	No No
Nightmares	2002UW09639	Nightmares	No	None	NA
Insomnia	2004UW17795	Insomnia	No	None	NA
SOC: Psychiatric disorders					
Attention deficit/hyperactivity disorder	2000UW05082[b]	Attention deficit/hyperactivity disorder	No	Aggression	No
Feeling abnormal	2003UW00170	Feeling abnormal	Yes	Medication error Psoriasis Eczema	Yes Yes Yes
Hallucination	1999UW00114	Hallucination	No	None	NA
Psychosis	2001UW04398	Psychotic disorder	No	None	NA
Regressiveness	2004UW20176	Regressive behaviour	No	None	NA
Suicide[a]	2004UW14830[b,c]	Suicide attempt	Yes	Anger Depression Anxiety Mood swings Obsessive thoughts Drug ineffective	No No No No No No
SOC: Renal and urinary disorders					

Table 14 Single report for serious or non-serious CDS unlisted topic (36 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Chromaturia	2001UW13042	Chromaturia	Yes	Dysuria	Yes
Proteinuria	2004UW15907	Proteinuria	No	None	NA
Incontinence	2000UW00819	Urinary incontinence	No	None	NA
Urinary retention	2003UW05704	Urinary retention	No	None	NA
Creatinine clearance ↓	1999UW04044	Creatinine renal clearance ↓	No	None	NA
SOC: Skin and subcutaneous tissue disorders					
Stevens-Johnson syndrome[a]	1999UW02930[d]	Stevens-Johnson syndrome	Yes	None	NA
Miscellaneous reports					
Autoimmune thyroiditis	2003UW14381	Autoimmune thyroiditis	No	None	NA
Abnormal lab test	2001UW09352	Laboratory test abnormal	No	None	NA
Malaise	2001UW02862	Malaise	No	None	NA
Aura	2003UW08620	Aura	No	None	NA
Chest discomfort	2004UW17710	Chest discomfort	No	Tachycardia	No
Discolored tooth	2002UW06955	Tooth discolouration	No	None	NA
Vomiting	2003UW07878	Vomiting	No	None	NA
Negative allergy test	2003UW14256	Allergy test negative	No	None	NA
Blood ALP increased	2003UW11013	Blood ALP increased	No	None	NA
Impaired healing	2004UW12914	Impaired healing	No	None	NA

[a,b,c,d] see sections 6.8, 6.13, 6.3, and 6.12, respectively for a discussion of these reports, CNS=central nervous system, EEG=electroencephalogram, ALP=alkaline phosphatase, ↑=increased.

Summary for single report for serious and non-serious CDS unlisted topics

For ear pain, tinnitus, pneumonia, septic shock, accidental exposure, arthropathy, rhabdomyolysis, CNS function test abnormal, EEG abnormal, paraesthesia, nightmares, insomnia, attention deficit hyperactivity disorder, feeling abnormal, psychotic disorder, regressive behavior, suicide attempt, chromaturia, proteinuria, creatinine renal clearance decreased, Stevens-Johnson syndrome, autoimmune thyroiditis, laboratory test abnormal, malaise, aura, tooth discoloration, allergy test negative, blood ALP increased, and impaired healing the reports involved a single report for each event (or topic). Therefore, no trends could be identified from these reports.

For hallucinations, urinary incontinence, urinary retention, headache, loss of consciousness, chest discomfort, and vomiting, although the event was reported as the primary preferred term in only one report, (1999UW00114, 2000UW00819, 2003UW05704, 2001UW11805, 2001UW01554, 2004UW17710, 2003UW07878, respectively) additional reports had the event listed as a secondary preferred term. The reports which had the event listed as a secondary preferred term include the following: "Hallucination, auditory" (2002UW03232), "Urinary incontinence" (2004UW01647)/"Incontinence" (2002SE04289), "Urinary retention" (2001UW01554), "Headache" (2001UW05539, 2001UW01554), "Depressed level of consciousness" (2001UW12073), "Chest pain" (2002AP02680), and "Vomiting" (2002UW01335). These reports were reviewed as an aggregate and no new significant safety information was identified.

5.4.4 Adolescents (age 12 to 18 years; 493 reports)

5.4.4.1 CDS listed topics, 183 reports

Multiple reports for CDS listed topic (177 reports)

Reports associated with CDS listed topics, that had multiple reports received are listed in Table 15 below.

Table 15 Multiple reports for CDS listed topic (177 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Blood and lymphatic disorders					
Leukopenia (19)	2004UW07545	Leukopenia	No	None	NA
	2004AP04879	Leukopenia	No	None	NA
	2003UW07563	Leukopenia	No	None	NA
	2003UW05252	Leukopenia	No	Hypothyroidism	No
	2003UW03376	Leukopenia	No	None	NA
	2003UW02493	Leukopenia	No	Rash	No
	2002AP02291	Leukopenia	Yes	Pyrexia Rash	Yes Yes
	2001SE08411	Leukopenia	No	None	NA
	2000UW03315	Leukopenia	No	None	NA
	2000UW00926	Leukopenia	No	Drug toxicity NMS Dehydration Conjunctivitis	No No No No
	1998UW49116	Leukopenia	No	None	NA
	2002UW10361	WBC count ↓	No	Neutrophil count ↓	No
	2002UW09421	WBC count ↓	No	None	NA
	2002UW01877	WBC count ↓	No	None	NA

Table 15 Multiple reports for CDS listed topic (177 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Leukopenia (19)	2002AP03145	WBC count ↓	No	None	NA
	2001UW15708	WBC count ↓	No	None	NA
	2000UW02160	WBC count ↓	No	None	NA
	2000AP01195	WBC count ↓	No	Polycythaemia Blood ALP ↑ Blood albumin ↑	No No No
	2003UW10805	WBC count ↓	No	None	NA
Neutropenia (9)	2004UW02209	Neutropenia	No	None	NA
	2002UW10875	Neutropenia	Yes	None	NA
	2002GB01084	Neutropenia	Yes	Leukopenia	Yes
	2001SE06486	Neutropenia	No	None	NA
	2001AP01996	Neutropenia	No	None	NA
	2000UW00663	Neutropenia	Yes	WBC count ↓ Lethargy	No No
	2002UW09985	Neutrophil count ↓	No	WBC count ↓	No
	2002UW03767	Neutrophil count ↓	No	WBC count ↓	No
	2001AP05426	Neutrophil count ↓	No	Platelet count ↓	No
SOC: Cardiac disorders					
Arrhythmias (9)	2004SE02575	Sinus tachycardia	Yes	Tachyarrhythmia Fatigue	Yes Yes
	2004UW18692[a]	Tachycardia	Yes	Depressed level of consciousness Hypotension Drug interaction Accidental overdose	Yes Yes Yes Yes
	2004SE02572	Tachycardia	Yes	Dizziness Syncope	Yes Yes
	2003UW00683	Tachycardia	No	Electrocardiogram abnormal	No
	2002GB01280	Tachycardia	No	None	NA
	2001UW07076	Tachycardia	No	None	NA
	2001UW00898	Tachycardia	No	None	NA
	2000AP05579	Tachycardia	Yes	None	NA
	1999UW01485	Tachycardia	No	None	NA

Table 15 Multiple reports for CDS listed topic (177 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Hypotension (5)	2000AP01571	Hypotension	No	Malaise Vomiting	No No
	2001UW03212	Hypotension	Yes	Syncope	Yes
	2001AP02345	Blood pressure decreased	No	Tachycardia	No
	2003UW02116	Orthostatic hypotension	No	Accident	No
	2004UW13260	Orthostatic hypotension	No	None	NA
Syncope (3)	2004PK01374	Syncope	Yes	Loss of consciousness Hypotension	Yes Yes
	2002UW02364	Syncope	No	None	NA
	2001UW10775	Syncope	Yes	Hypersomnia	Yes
SOC: Gastrointestinal disorders					
Constipation (2)	2003UW12445	Constipation	No	None	NA
	2003UW14071	Constipation	No	None	NA
SOC: General disorders					
Oedema (7)	2001UW13544	Pitting oedema	No	None	NA
	2004SE04437	Oedema peripheral	Yes	None	NA
	2004GB01322	Oedema peripheral	No	None	NA
	2003UW10169	Oedema peripheral	No	None	NA
	2003SE03930	Oedema peripheral	No	None	NA
	2001UW14363[b]	Oedema peripheral	No	Face oedema Dyskinesia	No No
	2001UW08040	Oedema peripheral	No	None	NA
Overdose[a] (15)	2003UW05590	Intentional overdose	Yes	Lethargy Ventricular tachycardia Hypoxia Tachypnea Infection Acute respiratory distress syndrome Pneumonia aspiration Pulmonary oedema	Yes Yes Yes Yes Yes Yes Yes Yes

Table 15 Multiple reports for CDS listed topic (177 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Overdose[a] (15)	2003AP01203[c]	Intentional overdose	Yes	Agitation Lethargy Hypotension Tachycardia	Yes Yes Yes Yes
	1998UW43530	Intentional overdose	No	Tachycardia	No
	2003UW10892[d]	Overdose[a]	Yes	None	NA
	2003UW13081	Overdose	Yes	Respiratory failure	Yes
	2004AC00231[c]	Overdose	Yes	Confusional state Agitation Hallucination Tachycardia	Yes Yes Yes Yes
	2004AP01560[e]	Overdose	Yes	Suicide attempt Depressed level of consciousness Rhabdomyolysis	Yes Yes Yes
	2004AP04794	Overdose	Yes	Coma Pneumonia	Yes Yes
	2004UW03645	Overdose	Yes	Drug toxicity	Yes
	2004UW07175	Overdose	Yes	Coma Convulsion	Yes Yes
	1999AP02940	Overdose	Yes	Somnolence	Yes
	2002UW13817[c,e]	Overdose	Yes	Suicide attempt Aggression Ventricular tachycardia	Yes Yes Yes
	2003UW02945	Overdose	Yes	Rash	Yes
	2004UW15638[d]	Drug toxicity	Yes	None	NA
	2002UW04875	Drug level increased	Yes	Drug interaction	Yes
SOC: Investigation					
Hepatic function abnormal (15)	1999UW03739	ALT ↑	No	None	NA
	2004GB01661	ALT ↑	Yes	None	NA
	2002SE03262	LFT abnormal	Yes	None	NA
	2001UW04331	LFT abnormal	No	None	NA
	2001AP01629	LFT abnormal	No	None	NA
	2004UW14515	LFT abnormal	No	None	NA
	2003GB02876	LFT abnormal	No	None	NA
	2000UW04416	Hepatic enzyme ↑ (ALT, AST)	No	None	NA

Table 15 Multiple reports for CDS listed topic (177 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Hepatic function abnormal (15)	2002UW00790	Hepatic enzyme ↑	No	Drug interaction Psychotic disorder	No No
	2004UW10964	Hepatic enzyme ↑	No	None	NA
	2004AP02670	Hepatic function abnormal	No	None	NA
	2000UW03088	Hepatic function abnormal	No	None	NA
	2003AP03768	Hepatic function abnormal	Yes	Pyrexia	No
	1999AP06235	Hepatocellular damage (ALT, GGT, AST)	Yes	Eosinophilia	Yes
	2001UW14389	Transaminases↑ (ALT, AST)	No	None	NA
Blood lipids (3)	2003SE03875	Blood cholesterol ↑	No	Blood triglycerides ↑	No
	2004UW19733	Blood cholesterol ↑	No	None	NA
	2003UW06451	Blood triglycerides ↑	No	None	NA
Weight gain[f] (15)	2001UW15552	Weight ↑	No	None	NA
	2001UW09625	Weight ↑	No	None	NA
	2000AP05542	Weight ↑	No	Blood ALP ↑	No
	2004UW17672	Weight ↑	No	None	NA
	2004UW07449	Weight ↑	No	None	NA
	2004PK00373	Weight ↑	Yes	None	NA
	2004AP01466	Weight ↑	No	None	NA
	2003UW14739	Weight ↑	No	None	NA
	2003UW13102	Weight ↑	No	None	NA
	2003UW07708	Weight ↑	No	None	NA
	2003UW00732	Weight ↑	No	None	NA
	2003AP04059	Weight ↑	No	Hypersomnia	No
	2003AP03696	Weight ↑	No	None	NA
	2002UW02962	Weight ↑	No	None	NA
	2002SE01178	Weight ↑	Yes	None	NA

SOC: Musculoskeletal and connective tissue disorders

Table 15 Multiple reports for CDS listed topic (177 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Muscle spasms and related cases (4)	2001UW07886[c]	Muscle rigidity	No	Agitation Tachycardia Hyperhidrosis	No No No
	2001AP03699	Muscle spasms	Yes	None	NA
	2004SE03153	Muscle spasms	No	Paraesthesia	No
	2001UW02955[b]	Muscle twitching	Yes	Dyskinesia Akinesia	Yes Yes
SOC: Nervous system disorders					
NMS (6)	2004UW11490	NMS	Yes	None	NA
	2003UW08176	NMS	Yes	None	NA
	2003PK01941	NMS	Yes	None	NA
	2002UW12184	NMS	Yes	None	NA
	2002SE05667	NMS	Yes	None	NA
	2001AP01429	NMS	Yes	None	NA
Somnolence (5)	2002GB01653[b]	Somnolence	Yes	Cogwheel rigidity Stiffness	Yes Yes
	1999UW03387[g]	Somnolence	unk	Diabetes mellitus non-insulin-dependent	unk
	2004UW20249	Somnolence	Yes	Vertigo	Yes
	2004UW09306	Somnolence	No	None	NA
	2003UW16160	Somnolence	No	None	NA
Tardive dyskinesia[h] (9)	2002UW09464	Tardive dyskinesia	Yes	None	NA
	2003UW02377	Tardive dyskinesia	Yes	None	NA
	2001UW02639	Tardive dyskinesia	No	None	NA
	1999AP00178	Tardive dyskinesia	No	None	NA
	2004UW18926	Tardive dyskinesia	Yes	None	NA
	2003UW15079	Tardive dyskinesia	No	None	NA
	2003UW14304	Tardive dyskinesia	Yes	None	NA
	2003UW05090	Tardive dyskinesia	Yes	None	NA
	2003UW12993	Tardive dyskinesia	Yes	None	NA
EPS[b] (31)	2003SE05619	Akathisia	No	Extrapyramidal disorder[g]	No
	2001UW15470	Akathisia	No	Restlessness	No
	2004UW17908	Akathisia	No	None	NA

Table 15 Multiple reports for CDS listed topic (177 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
EPS[b] (31)	2003UW11938	Buccoglossal syndrome	No	Tic	No
	1999UW01066	Dyskinesia	No	None	NA
	1998UW45328	Dyskinesia	Yes	None	NA
	1998UW45326	Dyskinesia	Yes	Chorea	Yes
	2004UW20560	Dyskinesia	No	None	NA
	2004UW05154	Dyskinesia	No	None	NA
	2004PK00903	Dyskinesia	Yes	None	NA
	2003UW08073	Dyskinesia	Yes	None	NA
	2003GB00460	Extrapyramidal disorder	No	Restlessness Vision blurred Anxiety Musculoskeletal stiffness Chromaturia Rigors	No No No No No No
	2004UW15310	Extrapyramidal disorder	No	None	NA
	2004SE04379	Extrapyramidal disorder	No	None	NA
	2003UW12294	Extrapyramidal disorder	No	None	NA
	2004UW07711	Extrapyramidal disorder	Yes	None	NA
	2001UW09830	Tremor	No	Dyskinesia	No
	2001UW06676	Tremor	No	None	NA
	1999UW03979	Tremor	No	Dyskinesia	No
	2002GB01559[f]	Masked facies	Yes	Weight increased Hypokinesia	Yes Yes
	2003SE00829	Drooling	No	Asthenia Dizziness	No No
	2003SE02715	Dystonia	Yes	None	NA
	2002GB01468	Dystonia	Yes	None	NA
	2001UW12872	Dystonia	No	None	NA
	2001UW12759	Dystonia	No	None	NA
	2001UW11258	Dystonia	No	Pain Crying	No No
	2001UW00734	Dystonia	No	None	NA

Table 15 Multiple reports for CDS listed topic (177 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
EPS[b] (31)	2000UW03450	Dystonia	Yes	Nausea Vomiting	Yes Yes
	1999UW00527	Dystonia	Unk	Eye rolling Dyskinesia	Unk Unk
	2003UW11925	Dystonia	No	Choreoathetosis	No
	2000UW00715	Dystonia	No	None	NA
Seizure disorder (12)	2003SE04650	Epilepsy	Yes	None	NA
	2004UW08444	Convulsion	Yes	None	NA
	2004UW05652	Convulsion	Yes	None	NA
	2002UW15128	Convulsion	Yes	None	NA
	2001SE06516	Convulsion	Yes	None	NA
	2001AP03064	Convulsion	Yes	None	NA
	2000UW04053	Convulsion	Yes	Syncope	Yes
	2001PK00036	Convulsion	Yes	None	NA
	2004SE03104	Grand mal convulsion	Yes	None	NA
	2002UW15293	Grand mal convulsion	Yes	None	NA
	2002GB02829	Grand mal convulsion	Yes	None	NA
	1998AP50548	Grand mal convulsion	Yes	Tachycardia Heart rate irregular Blood pressure ↑ Arrhythmia	No No No No
Sedation (6)	2002AP04499	Sedation	Yes	None	NA
	2001UW13023	Sedation	No	Dizziness Medication error	No No
	1999AP05733[f]	Sedation	No	↑appetite Weight ↑	No No
	2003UW14541[f]	Sedation	No	Weight ↑	No
	2003SE05890	Sedation	No	None	NA
	2002UW09601	Sedation	Yes	Headache Medication error	Yes Yes
SOC: Reproductive system and breast disorders					
Male urogenital (2)	2003UW01135	Priapism	Yes	None	NA
	2003UW02728	Priapism	Yes	None	NA

[a,b,c,d,e,f,g,h] see sections 6.14, 6.8, 6.13, 6.1, 6.3, 6.5, 6.2, and 6.7, respectively for further discussion of these reports, NMS=neuroleptic malignant syndrome, WBC=white blood cell, ALP=alkaline phophatase, LFT=liver function test, GGT=gamma-glutamyl transpeptidase, ↑=increased, ↓=decreased.

Summary for multiple reports for CDS listed topics

The AEs reviewed above are listed in the SEROQUEL CDS for the adult population. In addition to the reports in the table above, some reports were received that contained events reported at the secondary preferred term level (not the first event reported) for the topics covered in this table. The reports which had an event listed as a secondary preferred term include the following: "Weigh increased" (2004UW12118, 2004UW11289, 2004AC00232, 2003UW16130, 2003UW14541, 2003UW14488, 2003SE04649, 2002UW14927, 2002UW10888, 2002GB01559, 2001UW00231, 2001AP05884, 2001AP05633, 1999AP05792, 1999AP05733, 1999AP04948), "Dyskinesia" (2001UW14363, 2001UW09830, 2001UW02955, 1999UW03979, 1999UW00527), "Extrapyramidal symptoms" (2004AC00232, 2003SE05619), "Akathisia" (2004SE00244, 2004AC00232, 2003UW09050), "Dystonia" (2003UW16728), "Cogwheel rigidity" (2002GB01653), "Intentional overdose" (1998UW43530, 2003AP01203, 2003UW05590), "Overdose" (2001AP00830), "Accidental overdose" (2004UW18692), "Convulsion" (2004UW07175, 2004UW04388), "Leukopenia" (2002GB01084, 2004UW04388), "Tachycardia"/"Sinus tachycardia" (2003AP01203, 2001UW07886, 2003GB02730, 2004AC00231, 2001AP00830, 2003UW14113, 2003SE04433, 2001AP02345, 1998UW43530, 2003UW16449, 1998UW47187, 1998AP50548, 2004SE02575), "Hypotension" (2003AP01203, 1998AP46181, 2004UW18692, 2004PK00544, 2004PK00234, 2004PK01374, 2001AP00830), "Syncope" (2001UW03212, 2000UW04053, 2003SE02572), "Constipation" (2002UW08543, 2003UW12724, 2003GB00456), "Oedema peripheral" (1998UW49352, 199UW49353, "Drug toxicity" (describing overdose) (2004UW03645), "Liver function test abnormal" (2000AP03966, 2002UW17056), "Blood triglycerides increased" (2001AP05884, 2003SE03875), "Neutrophil count decreased" (2002UW17056, 2002UW10361), "White blood cell count decreased" (2002UW17056, 2002UW09985, 2002UW03767, 2000UW00663), "Muscle twitching" (2003UW14113), "Neuroleptic malignant syndrome" (2000UW00926), "Somnolence" (2004SE00244, 2004UW04448, 2003GB03350, 1999AP02940, 1999AP04980, 2003UW14113), "Hepatic enzyme increased" (2003UW12724), "Sedation" (2004UW04394, 1998UW47387, 2002UW09599, 2003SE04649, 2001AP05633).

For further information on the reports of "Weight increased," see Section 6.5 *Topics of interest; Weight Gain*. For further information on the reports of "Dyskinesia," "Extrapyramidal symptoms," "Akathisia," and "Dystonia" see Section 6.8 *Topics of interest; Extrapyramidal symptoms*. For further information on the reports of "Overdose," "Intentional overdose," and "Accidental overdose" see Section 6.14 *Topics of interest; Overdose*.

Following a review of all these reports of events (at the primary and secondary level) that are listed in the SEROQUEL CDS for the adult population, it was determined that there was no

difference in frequency, severity, or characteristics of these events when compared to the known profile of SEROQUEL in adults.

Single reports for serious and non-serious CDS listed topics (6 reports)

The reports associated with a CDS listed topic for which there were only a single report received are contained in Table 16 below.

Table 16 Single report for CDS listed topics (6 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Investigations					
Lab tests	2002SE03136	Thyroxine ↓	No	None	NA
	2002UW13689	Eosinophil count ↑	No	None	NA
SOC: General disorders and administration site conditions					
Drug interaction	2000UW04135	Drug interaction	No	Aggression Hostility	No No
SOC: Immune system disorders					
Hypersensitivity	2004UW20371	Hypersensitivity	No	None	NA
SOC: Nervous system disorders					
Nervous system disorder	2002GB01501	Trismus	Yes	Muscle spasticity	Yes
Nervous system disorder	2002UW09599	Dizziness	No	Sedation Chest pain Medication error	No No No

[a] see section 6.13 for a discussion of this report, ↓=decreased, ↑=increased.

Summary for single reports for serious and non-serious CDS listed topics

For "Thyroxine decreased," "Hypersensitivity," and "Trismus," the reports involved a single report for each event (or topic). Therefore, no trends could be identified from these reports.

For "Dizziness" although the event was reported as the primary preferred term in only one report, 11 additional medically confirmed reports had the event listed as a secondary preferred term (2003SE00829, 2003GB00226, 2003UW12724, 2002UW09570, 2001UW13023, 2004SE02572, 2003SE00244, 2004SE04136, 2003UW16728, 1998UW47187, and 2004SE04540).

For "Drug interaction" although the event was reported as the primary preferred term in only one report, four additional medically confirmed reports of "Drug interaction" had the event listed as a secondary preferred term (2004UW18692, 2002UW00790, 1998UW47387, 2002UW04875). One report (2004UW18692) described a patient who accidentally took SEROQUEL 900 mg/day (prescribed dose 600 mg/day) with a prescribed dose of

erythromycin (333 mg/day). The following day, the patient experienced tachycardia, decreased level of consciousness, and hypotension. The patient's toxicity screen revealed only high levels of tricyclic antidepressants. The patient recovered.

Another report (2002UW00790) described a patient who had been receiving SEROQUEL 800 mg/day for one year. Concomitant medication topiramate (dose unspecified) was started, and the liver enzymes elevated to three times the normal value. SEROQUEL was reduced to 400 mg/day, and after several days, the liver enzymes returned to normal. However, the patient's psychosis grew worse on the lower dose of SEROQUEL. No further information was provided. Another report (1998UW47387) described a patient who experienced gastrointestinal distress, paraesthesia, sedation, and pain (physical aches) after SEROQUEL was increased to 200 mg/day (initial dose unspecified). The patient was a long-term user of fluoxetine, and the physician was concerned about a possible drug interaction. The outcome was not provided. Another report (2002UW04875) described a patient who had been on SEROQUEL (50 mg/day), which was increased to 100 mg/day. Concomitant medications consisted of clobazam and valproate. When the dose of SEROQUEL was increased, the patient experienced increased levels of valproate, and the physician decreased the dose of the valproate. The patient did not experience any signs or symptoms of valproate toxicity. No further information was provided.

These reports of drug interaction demonstrated no consistent pattern(s) for any of the possible interacting drugs. For most of these reports, information was not provided to confirm altered blood levels, effects on metabolism, or excretion of reported interacting drugs. In view of the incomplete nature of these reports an actual drug interaction cannot be ascertained.

The AEs reviewed above are listed in the SEROQUEL CDS for the adult population. Following a review of these reports, it was determined that there was no difference in frequency, severity, or characteristics of these events when compared to the known profile of SEROQUEL in adults.

5.4.4.2 CDS unlisted topics (310 reports)

Multiple reports for CDS unlisted serious topics (55 reports)

Multiple reports for CDS listed serious topics including suicide, glucose dysregulation, prolonged QT, arrhythmias and EKG abnormalities, hypertension, pericardial effusion, mania, cataract, deep vein thrombosis, pregnancy related events, decreased platelet counts, vision impaired, conjunctivitis, thyroid and thyroid hormone abnormalities, vomiting, nausea, abdominal pain, drug ineffective, drug interaction, pyrexia, temperature dysregulation, blood creatine phosphokinase increased, muscle and joint pain, hypoesthsia, parathesia, myoclonus, headache, abnormal behavior, behavior and socialization disturbances, schizophrenia and psychiatric disorders, hyperphagia, sleep disorders, tic, urinary incontinence and retention, hyperprolactinaemia and related disorders, other breast disorders, menstruation irregularities, epistaxis, rash, skin discoloration, face edema, hyperhydrosis, alopecia, blister, are contained in different tables in the following sections. Reports of suicide are contained in Table 17 below.

Table 17 Multiple reports for serious CDS unlisted topics—Suicide[a] (5 reports)

Topic	Report	Age/ Sex	Dose/ TTO	Medical History	Concomitant Medicine	PTs/Comment
SOC: Psychiatric disorders						
Suicide (5)	2001AP05211 Serious	16/Unk	Dose/TTO unk	Not provided	Valproate, bupropion	PTs: Completed suicide. Pt intentionally ingested Seroquel, valproate, and bupropion simultaneously. Doses not reported. Pt died. No further info.
	2004UW09606 Serious	14/F	600-800 mg /day; TTO unk	Not provided	Not provided	PTs: Suicidal ideation, Muscular weakness, Balance disorder. Seroquel dose ↑. Pt hospitalized for events x 7 days. No further info.
	2001UW06751[b] Serious	17/Unk	Dose/TTO unk	Not provided	Paroxetine[c]	PTs: Completed suicide. Pt died.
	2004UW06809 Serious	14/M	Dose/TTO unk	Bipolar disorder, mental disorder, attention deficit/hyperactivity disorder	Not provided	PTs: Suicidal ideation. Pt hospitalized. Seroquel D/c'd. No further info.
	2001AP00830 Serious	17/M	One-time dose (12 grams)	Impulse-control disorder, depression, anxiety, personality disorder, drug abuser, agitation	Gabapentin, sertraline[c], clonazepam	PTs: Suicide attempt, Overdose, Hypotension, Blood creatine phosphokinase increased, Coma, Tachycardia. Pt ingested 12 g Seroquel; was hospitalized. Tx activated charcoal (No intubation). Rec'd 2 days later.

[a,b] see sections 6.3 and 6.1, respectively for further discussion of these reports, [c] for which increased suicidal ideation in children and adolescents has been reported, unk=unknown, info=information, ↑=increased, D/c'd = discontinued, tx=treatment, rec'd=recovered.

Summary for suicide

Further information on these reports and suicide can be found in Section 6.3 *Topics of interest; Suicide*. Narratives for the serious reports for this topic can be found in Appendix B.

AstraZeneca believes that these reports of suicide/suicide attempts and suicidal ideation reflect the background incidence of these events in the schizophrenic and manic populations. There is no signal to suggest that patients using SEROQUEL are at an increased risk for suicide attempt as a consequence of SEROQUEL therapy or that a causal relationship exists between SEROQUEL therapy and suicide attempt.

Reports associated with glucose dysregulation are contained in Table 18 below.

Table 18 Multiple reports for serious CDS unlisted topic—Glucose dysregulation[a] (15 reports)

Topic	Report	Age/ Sex	Dose/ TTO	Medical History	Concomitant medications	PTs/Comment
SOC: Metabolism and nutrition disorders						
Glucose dysregulation (15)	2002UW05916[b] Serious	-	-	-	-	PTs: Diabetic hyperosmolar coma, DM non-insulin dependent, Renal failure acute, Leukoencephalopathy, Cardiomegaly, Brain oedema, Hyperthermia, Infection, Mental status changes, Blood pressure ↑, Pharyngolaryngeal pain, Abdominal pain, Leukocytosis. See section 6.2 *Glucose dysregulation*
	2003GB01346[b] Serious	-	-	-	-	PTs: DKA, Tinea cruris See section 6.2 *Glucose dysregulation*
	2001UW00231[c] Serious	-	-	-	-	PTs: DM, Weight ↑. See section 6.2 *Glucose dysregulation*
	2002AP04001 Serious	-	-	-	-	PT: DM See section 6.2 *Glucose dysregulation*
	2000UW00266 Serious	-	-	-	-	PT: DM See section 6.2 *Glucose dysregulation*
	1999UW00967 Non-serious	-	-	-	-	PT: DM See section 6.2 *Glucose dysregulation*
	2002AP01607 Serious	-	-	-	-	PTs: DM non-insulin dependent[a], Blood glucose abnormal, Hyperlipidemia. See section 6.2 *Glucose dysregulation*
	2002UW12946 Non-serious	-	-	-	-	PT: DM inadequate control See section 6.2 *Glucose dysregulation*
	2004GB00610 Serious	-	-	-	-	PT: DKA See section 6.2 *Glucose dysregulation*
	2000UW02905 Serious	-	-	-	-	PTs: DKA, Pancreatitis acute, Lipids ↑. See section 6.2 *Glucose dysregulation*

Table 18 Multiple reports for serious CDS unlisted topic—Glucose dysregulation[a] (15 reports)

Topic	Report	Age/ Sex	Dose/ TTO	Medical History	Concomitant medications	PTs/Comment
Glucose dysregulation (15)	2004UW18892 Non-serious	-	-	-	-	PT: Blood insulin ↑ See section 6.2 *Glucose dysregulation*
	2004UW15170 Non-serious	-	-	-	-	PT: Blood glucose ↑ See section 6.2 *Glucose dysregulation*
	2004UW04671 Serious	-	-	-	-	PT: Blood glucose ↑ See section 6.2 *Glucose dysregulation*
	2002UW14424 Non-serious	-	-	-	-	PT: Blood glucose ↑ See section 6.2 *Glucose dysregulation*
	2002UW14927[c] Non-serious	-	-	-	-	PTs: Hyperglycaemia, Weight ↑ See section 6.2 *Glucose dysregulation*

[a,b,c] see sections 6.2, 6.1, and 6.5 for further discussion of these reports, ↑=increased, DKA=diabetic ketoacidosis.

Summary for glucose dysregulation

Further information on this topic can be found in Section 6.2 *Topics of interest; Glucose dysregulation*. Narratives for serious events in this topic can be found in Appendix B.

These reports were confounded by the patient's concomitant medical conditions, concomitant medications, or both, or provided insufficient information for analysis. Thus, they do not establish a causal relationship between glucose dysregulation and SEROQUEL and disclosed no new significant safety information about the use of SEROQUEL.

Reports associated with cardiac disorders are contained in Table 19 below.

Table 19 Multiple reports for serious CDS unlisted topic—Cardiac disorders (17 reports)

Topic	Report	Age/ sex	Dose/ TTO	Medical History	Concomitant medications	PTs/Comment
SOC: Cardiac disorders						
Prolonged QT[a] (4)	2004UW02024 Non-serious	-	-	-	-	PTs: ECG QT corrected interval See section 6.6 *Prolonged QT*
	2003UW05255 Serious	-	-	-	-	PTs: ECG QT corrected interval See section 6.6 *Prolonged QT*
	2003GB00456 Serious	-	-	-	-	PTs: ECG QT prolonged, Palpitations, Blood pressure ↑, Constipation See section 6.6 *Prolonged QT*
	2002UW09570 Serious	-	-	-	-	PTs: ECG QT prolonged, Dizziness, Medication error See section 6.6 *Prolonged QT*
Arrhythmias + ECG abnormalities (7)	2000UW03962[b,c] Serious	-	-	-	-	PTs: Arrhythmia, Pulmonary oedema, Pulmonary congestion, Agitation See section 6.1 *Reports with an outcome of death*
	2001UW14447[d] Serious	13/M	300 mg/day; one day	Morbid obesity	Valproate	PTs: Arrhythmia, Myocardial ischemia, DKA After 1 day of therapy w/ Seroquel Pt had arrhythmia that progressed to ischemia. Tx=stress test + cardiac catheterization was scheduled. Approx 1 month later, Pt had DKA. Tx=insulin. Seroquel + valproate contd.
	2004PK00234 Non-serious	14/F	25 mg/day; 1 day	Not provided	Not provided	PTs: Bradycardia, Hypotension After Pt started Seroquel Pt had bradycardia + hypotension. Seroquel d/c'd. Pt rec'd. No other info.
	1999UW00267 Serious	?/M	Dose/TTO unk	Not provided	Not provided	PT: Heart rate irregular Pt had irregular heart rate after starting Seroquel. Pt outcome + if Seroquel contd unk. No other info.

Table 19 Multiple reports for serious CDS unlisted topic—Cardiac disorders (17 reports)

Topic	Report	Age/ sex	Dose/ TTO	Medical History	Concomitant medications	PTs/Comment
Arrhythmias + ECG abnormalities (7)	2003SE04433 Non-serious	18/M	1000 mg/ day; 7 days	Not provided	Diazepam	PTs: ECG repolarization abnormality, Tachycardia Day 7: ECG repolarization abnormality + tachycardia. Seroquel dose ↓, ECG repolarization abnormality resolved, however tachycardia did not. Seroquel d/c'd. No further info.
	1999AP05764 Non-serious	17/M	100 mg/ day; TTO unk	Not provided	Not provided	PTs: Bundle branch block Pt experienced BBB. Seroquel contd. Outcome unk. No other info.
	2001UW01167 Non-serious	13/F	Dose/TTO unk	Not provided	Benzatropine[e], lithium[f]	PTs: ECG abnormal Pt had abnormal ECG (unspecified). Pt outcome + if Seroquel contd unk. No other info.
Hypertension (4)	2003GB01919 Serious	16/F	300 mg/day; dose unk	Not provided	Risperidone	PTs: Blood pressure ↑ Pt had HTN one day after Seroquel ↑ to 300 mg/day. Tx=anti-hypertensives, ECG. Seroquel d/c'd on day 5. Pt rec'd. No other info.
	2002SE01362 Serious	14/M	125 mg/ day; 34 days	Maple syrup urine disease	Pseudoephedrine[g], clonazepam, amoxicillin	PTs: HTN, Speech disorder, Ataxia. Pt experienced HTN, speech disorder + ataxia. Seroquel d/c'd. Pt rec'd. No other info.
	2000UW00561 Non-serious	17/M	Dose/TTO unk	Not provided	Lithium	PTs: HTN Pt experienced HTN. Tx=clonidine. Seroquel contd. Pt not yet rec'd. No other info.
	1998UW47187 Non-serious	18/M	200 mg/ day: TTO unk	Not provided	Lithium	PTs: Blood pressure ↑, Tachycardia, Dizziness, Asthenia, Anxiety, Feeling hot Pt had AEs after unk time on Seroquel. Seroquel dose ↑ to 600 mg/day. Pt also receiving lithium. Seroquel contd. No further info
Pericardial effusion (2)	2002GB00696 Serious	17/F	300 mg/ day; TTO 6 days	Esophageal reflux, anorexia nervosa	Ranitidine, mirtazapine	PT: Pericardial effusion After 2 mos on Seroquel Pt had abnormal ECG. Dose of Seroquel ↑. 6 days later Pt had pericardial effusion. Seroquel d/c'd. Pt not yet rec'd. No further info.

Table 19 Multiple reports for serious CDS unlisted topic—Cardiac disorders (17 reports)

Topic	Report	Age/ sex	Dose/ TTO	Medical History	Concomitant medications	PTs/Comment
Pericardial effusion (2)	2003UW01894 Serious	14/F	400 mg/ day; TTO unk	Not provided	Not provided	PT: Pericardial effusion Pt developed pericardial effusion after starting Seroquel. occurred after Pt started Seroquel. Event was resolving. Unk if Seroquel contd. No further info.

[a,b,c,d] see sections 6.6, 6.1, 6.13, and 6.2, respectively for further discussion of these reports, [e] for which arrhythmias have been reported, [f] for which AV block and ventricular arrhythmias have been reported, [g] for which hypertension has been reported, mos = months, ↑ = increased, unk or ? = unknown, ECG = electrocardiogram, D/c'd = discontinued, tx = treatment, w/ = with, IV = intravenous, contd = continued, info = information, DKA = diabetic ketoacidosis, approx = approximately, hosp = hospitalized,

Summary for cardiac disorders

Narratives for serious events for this topic can be found in Appendix B.

Further information on this topic and these four reports (2002UW09570; "Electrocardiogram QT prolonged," 2003UW05255; "Electrocardiogram QT prolonged," 2004UW02024, 2003GB00456; both "Electrocardiogram QT prolonged") can be found in Section 6.6 *Topics of interest; Prolonged QT.*

Of the seven reports of arrhythmia or ECG abnormalities, one fatal report (2000UW03962; "Arrhythmia") was confounded by concomitant medications (haloperidol, for which ventricular arrhythmias have been reported, and benztropine, for which arrhythmias including supraventricular tachycardia, atrioventricular dissociation and paradoxical sinus bradycardia have been reported). In addition, this report was confounded by the patient's history of catecholamine-induced arrhythmia and non-compliance with prescribed medications (propranolol). Further information on this report can be found in Section 6.1 *Topics of interest; Reports with an outcome of death.* Another report (2001UW14447; "Arrhythmia") was confounded by the patient's history of morbid obesity. The report described a patient who developed ischemia (identified with a stress test) secondary to arrhythmia. Conflicting information indicated that the patient did not have symptoms of cardiac ischemia. At the time of the report, the patient was scheduled for a cardiac catheterization. No further information was available.

Another two reports that were confounded by concomitant medications: 2003SE04433 ("Electrocardiogram repolarisation abnormality") diazepam, for which for which respiratory depression and hypotension occasionally occur with high dosage and parenteral administration, 2001UW01167 ("Electrocardiogram abnormal") benzatropine, for which arrhythmias including supraventricular tachycardia, atrioventricular dissociation and paradoxical sinus bradycardia have been reported and lithium, for which ventricular arrhythmia, atrioventricular block, cardiac conduction abnormalities, sinus node dysfunction, bradycardia, and lithium toxicity resulting in QT prolongation or death have been reported.

The remaining three reports (2004PK00234; "Bradycardia," 1999UW00267; "Heart rate irregular," 1999AP05764; "Bundle branch block") contained scant clinical detail and did not lend itself to analysis.

One additional medically confirmed report had "Electrocardiogram abnormal" listed as a secondary preferred term (2003UW00683). This report was confounded by a concomitant medication (venlafaxine), for which orthostatic hypotension, syncope, palpitations, arrhythmias, and tachycardia have been reported.

One additional medically confirmed report had "Bradycardia" listed as a secondary preferred term (1998AP46181). This report described a patient who experienced a drop in blood pressure, lowered pulse rate, decreased respiration rate, and collapse 15 minutes after taking SEROQUEL. The patient had a chronic history of drug sensitivity. SEROQUEL was discontinued and the patient recovered. This report was confounded by concomitant

medications (chlorpromazine, for which tachycardia, cardiac arrhythmias, hypotension, ventricular arrhythmias, sudden death, Q and T wave distortions, and shock have been reported; zuclopenthixol, for which sudden death, Q and T wave distortions, and shock have been reported; and haloperidol, for which ventricular arrhythmias, sudden death, Q and T wave distortions, and shock have been reported). The opposite of bradycardia (tachycardia) is an expected physiological response to the alpha-adrenergic blocking property of SEROQUEL. In fact, tachycardia is a common ADR for SEROQUEL.

One additional medically confirmed report had "Heart rate irregular" listed as a secondary preferred term. This report (1998AP50548) described a patient who experienced life-threatening tonic-clonic seizure while taking SEROQUEL. The SEROQUEL dose was adjusted and the patient refused food or drink and experienced tachycardia, arrhythmia, and increased blood pressure. SEROQUEL was discontinued and the patient recovered. Upon re-introduction to SEROQUEL therapy, the patient experienced no adverse reaction. No further information was available.

Two of the reports of hypertension were confounded by concomitant medications: 2003GB01919, "Blood pressure increased"; risperidone, for which orthostatic hypotension, hypertension, QT prolongation resulting in death, atrioventricular block, ventricular extrasystoles, ventricular tachycardia, and MI have been reported, and 2002SE01362, "Hypertension"; pseudoephedrine, for which tachycardia has been reported. Another report (2000UW00561, "Hypertension") contained scant clinical detail and thus could not be analyzed. Another report (1998UW47187, "Blood pressure increased") described an 18-year old patient who experienced blood pressure increased, dizziness, weakness, tachycardia while receiving SEROQUEL and lithium. SEROQUEL was continued. No further information was provided.

Five additional medically confirmed reports had "Blood pressure increased" listed as a secondary preferred term (2002UW05916, 2003GB00456, 1998AP50548, 2001UW12881, 2003UW16449). Two of the reports were already discussed because they also had primary preferred terms identifying events of diabetic hyperosmolar coma (2002UW05916) and electrocardiogram QT prolonged (2003GB00456; scant report). The third report (1998AP50548) was already discussed above in this section because it also had a secondary event of heart rate irregular. The fourth report (2001UW12881) described a patient who experienced a tightness and tingling sensation in her throat, shortness of breath, and blood pressure increased after taking SEROQUEL and diphenhydramine. The patient recovered five hours later. No further information was available. The final report (2003UW16449) described a patient who experienced a racing heart, chest pain, and elevated blood pressure after taking SEROQUEL and fluoxetine. No further information was available. This report was confounded by concomitant medication fluoxetine, for which orthostatic hypotension has been reported. The opposite of hypertension (hypotension) is an expected physiological response to the alpha-adrenergic blocking property of SEROQUEL. In fact, hypotension is a common ADR for SEROQUEL.

Of the two reports of pericardial effusion, one report (2002GB00696; "Pericardial effusion") described a 17-year-old patient who weighed 35.8 kilogram and experienced an undefined EKG abnormality after two months of SEROQUEL. Six days later the patient developed pericardial effusion. SEROQUEL was discontinued and the event was ongoing one month later. The other report (2003UW01894; "Pericardial effusion") contained scant clinical detail and did not lend itself to analysis. Taken together, these reports provided insufficient information for clinical analysis. Thus, they do not establish a causal relationship between cardiac disorders and SEROQUEL.

Reports of cataracts are contained in Table 20 below.

Table 20 Multiple reports for CDS unlisted serious topic—Cataract (12 reports)

Topic	Report	Age/ sex	Dose/TTO	Medical History	Concomitant medications	PTs/Comment
SOC: Eye disorders						
Cataract (12)	2001UW08694 Serious	-	-	-	-	PTs: Cataract See section 6.9 *Cataract*
	2001UW07040 Serious	-	-	-	-	PTs: Bilateral cataracts See section 6.9 *Cataract*
	2001UW06912 Serious	-	-	-	-	PTs: Cataract See section 6.9 *Cataract*
	2001UW04295 Serious	-	-	-	-	PT: Posterior capsule opacification. See section 6.9 *Cataract*
	2004UW08477 Non-serious	-	-	-	-	PT: Cataract. See section 6.9 *Cataract*
	2004UW02895 Non-serious	-	-	-	-	PT: Cataract. See section 6.9 *Cataract*
	2004UW01291 Non-serious	-	-	-	-	PT: Bilateral cortical cataracts See section 6.9 *Cataract*
	2003UW11378 Non-serious	-	-	-	-	PT: Cataract. See section 6.9 *Cataract*
	2003UW03542 Non-serious	-	-	-	-	PTs: Cataract cortical, Cataract subcapsular. See section 6.9 *Cataract*
	2001UW16257 Non-serious	-	-	-	-	PT: Cataract. See section 6.9 *Cataract*
	2000UW00840 Non-serious	-	-	-	-	PT: Lenticular opacities See section 6.9 *Cataract*
	1999UW00052 Non-serious	-	-	-	-	PTs: Bilateral cataracts, Blurred vision See section 6.9 *Cataract*

Summary for cataract

Further information on these reports can be found in Section 6.9 *Topic of interest; Cataract*. Narratives for these reports can be found in Appendix B.

Taken together, these reports were confounded by concomitant medications or medical history, described insufficient drug exposure time, or provided insufficient information for clinical analysis. Thus, they do not establish a causal relationship between cataract and SEROQUEL use in children.

Reports of deep vein thrombosis are contained in Table 21 below.

Table 21 Multiple reports for serious topic—Deep vein thrombosis (2 reports)

Topic	Report	Age /sex	Dose; TTO	Medical History	Concomitant Medicine	PTs/Comment
SOC: Vascular disorders						
Deep vein thrombosis (2)	2003UW16602 Serious	14/F	Dose/TTO unk	Not provided	Escitalopram	PTs: Deep vein thrombosis Believed to be d/t clotting disorder. Pt outcome + if Seroquel contd unk. No other info.
	2003PK02175 Serious	14/ M	500 mg/day; 19 days	Mental retardation, acute polymorphic psychogenic disorder, schizophreniform disorder w/ catatonic symptoms	Pipamperone, lorazepam, risperidone	PT: Deep vein thrombosis. Day 19: DVT. Tx=phenprocoumon + surgical hose. Seroquel contd + increased to 800 mg/day ~2 months later. Pt not yet rec'd.

? or unk = unknown, w/ = with, info = information, contd. = continued

Summary for deep vein thrombosis

Narratives for serious events in this topic can be found in Appendix B. Of the two reports of deep vein thrombosis, one report (2003UW16602) was believed due to a clotting disorder. Medical history was unknown for this patient and no further information was provided. The second report (2003PK02175) described a patient with a history of catatonia who developed a deep vein thrombosis (DVT). Therapy with SEROQUEL was continued at a higher dose and at the time of the report the patient had not yet recovered. The patient's catatonia might have contributed to the development of the DVT.

These reports were confounded by concurrent medical conditions and provided limited information for more in depth clinical analysis. Thus, they do not establish a causal relationship between deep vein thrombosis and SEROQUEL and disclosed no new significant safety information about the use of SEROQUEL in children.

Pregnancy related reports are contained in Table 22 below.

Table 22 Multiple reports for serious topic—Pregnancy related cases (4 reports)

Topic	Report	Age/ Sex	Dose/TTO	Medical History	Concomitant Medication	PTs/Comment
SOC: Pregnancy, puerperium, and perinatal conditions						
Pregnancy related reports (4)	2002GB00788 Serious	17/F	300 mg/day; >1 years	Smoker, chemical abuser, drug abuser, psychotic family member	Not provided	PTs: Abortion spontaneous, Drug exposure during pregnancy. 2 mos after Pt became pregnant, Pt began bleeding. Scan showed no fetal growth. Pt had spontaneous miscarriage. Seroquel contd. No further info.
	2003UW02480 Serious	17/F	600 mg/day; 2 years 8 mos	Depression	Bupropion[a]	PT: Abortion spontaneous. Pt became pregnant. Seroquel + bupropion D/c'd. 10 days later Pt had spontaneous miscarriage. No further info.
	2002GB01105 Serious	15/F	300-700 mg/ day; 2 mos	Asthma, smoker, drug abuser, psychosis	Fluvoxamine, fluoxetine, lorazepam	PTs: Drug exposure during pregnancy, Pre-eclampsia, Prolonged labor, Nosocomial infection. At some point, fluvoxamine switched to fluoxetine and Seroquel ↑ to 700 mg/day. When pregnancy discovered, Seroquel ↓ to 300 mg/day. Pt had pre-eclampsia; was hospitalized (2 weeks). Labor induced. Prolonged labor led to emergency C-section. Mother acquired infection. Baby had edema, jaundice, breathing/feeding difficulties associated with hospital-acquired infection. Tx for baby included IV antibiotics. Baby rec'd after 7 days. No outcome for mom and no further info.
	1998UW43854 Non-serious	17/F	25-50 mg/day; 53 days	bipolar disorder	Fluoxetine	PT: Pregnancy. Outcome + if Seroquel contd is unk. No other info.

[a] for which breast feeding and pregnancy are contraindicated, mo(s)=month(s), d/c'd=discontinued, info=information, c-section=caesarean section, tx=treatment, IV=intravenous, rec'd=recovered, contd=continued.

Summary for pregnancy related cases

Narratives for serious events in this topic can be found in Appendix B.

Of the four reports related to pregnancy, one non-serious report (1998UW43854; "Pregnancy") contained scant clinical detail (including no outcome) and did not lend itself to analysis. Another serious report (2002GB01105; "Drug exposure during pregnancy") was confounded by the patient's lifestyle, which included smoking and drug abuse. The baby recovered from the hospital-acquired infection and no outcome was provided for the mom.

One serious report (2002GB00788; "Abortion spontaneous") was confounded by the patient's lifestyle, which included smoking and abuse of drugs and other chemicals. Concomitant medications were not reported. The last serious report (2003UW02480; "Abortion spontaneous") was confounded by the patient's use of bupropion, for which pregnancy is contraindicated.

These reports were confounded by concomitant medications or unhealthy lifestyle including drug abuse or provided insufficient information for clinical analysis. Thus, they did not establish a causal relationship between these pregnancy-related AEs including spontaneous abortion and SEROQUEL. They disclosed no new significant safety information about the use of SEROQUEL in pregnant children.

Multiple reports for non-serious CDS unlisted topics (174 reports)

Reports of mania are contained in Table 23 below.

Table 23 Multiple reports for non-serious topic—Mania (4 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Psychiatric disorders					
Mania (4)	2004GB00448	Mania	No	None	NA
	2002UW02399	Mania	No	None	NA
	2002UW02353	Mania	No	None	NA
	1998UW49785	Mania	No	Thyroid disorder	No

Summary for mania

All four reports of "Mania" (2004GB00448, 2002UW02399, 2002UW02353, 1998UW49785) contained scant clinical detail and did not lend themselves to analysis.

These reports provided insufficient information for analysis. They do not establish a causal relationship between mania and SEROQUEL and disclosed no new significant safety information about the use of SEROQUEL in children.

Reports of decreased platelet count are contained in Table 24 below.

Table 24 Multiple reports for non-serious CDS unlisted topics—Decreased platelet count (2 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Blood and lymphatic system disorders					
Decreased platelet counts (2)	2003GB01453	Platelet count decreased	No	None	NA
	2004UW03555[a]	Thrombocytopenia	No	Abnormal behavior	No

[a] see section 6.13 for further description of this report.

Summary for decreased platelet counts

These two reports (2003GB01453; "Platelet count decreased," 2004UW03555; "Thrombocytopenia") contained scant clinical detail and did not lend themselves to analysis.

Two additional medically confirmed reports had "Platelet count decreased" listed as a secondary preferred term (2003UW00519, 2001AP05426). Both of these reports contained scant clinical detail and did not lend themselves to analysis.

These reports provided insufficient information for clinical analysis. Thus, they do not establish a causal relationship between decreased platelet count and SEROQUEL and disclosed no new significant safety information about the use of SEROQUEL in children.

Reports of eye disorders are contained in Table 25 below.

Table 25 Multiple reports for non-serious CDS unlisted topics—Eye disorders (6 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Eye disorders					
Vision impaired (4)	2004SE05049	Visual acuity reduced	Yes	None	NA
	2003UW16254[a]	Vision blurred	Yes	Thinking abnormal Abnormal behavior	No No
	2002UW06793	Vision blurred	No	Visual acuity reduced	No
	1998UW48873	Vision blurred	No	None	NA
Conjunctivitis (2)	2004UW11552	Conjunctivitis	No	None	NA
	2002UW06135	Conjunctivitis	No	None	NA

[a] see section 6.13 for further description of this report.

Summary for eye disorders

Of the three reports of "Vision blurred," one report (2003UW16254) was confounded by a concomitant medication (aripiprazole), for which pigmentary retinopathy, corneal and lens opacities have been reported. Additionally, this report was confounded by the patient's medical history of wearing corrective lenses. Another report (2002UW06793; also contained

event of "Visual acuity reduced") was confounded by a concomitant medication (fluoxetine), for which abnormal vision has been reported. No further information was provided. Another report (1998UW48873) was confounded by a concomitant medication (carbamazepine), for which lenticular opacities and visual disturbances have been reported. No further information was provided for any of these reports. The one report of "Visual acuity reduced" (2004SE05049) was confounded by a concomitant medication (oxcarbazepine), for which nystagmus and diplopia have been reported. Further information was not available for additional analysis.

One additional medically confirmed report had "Vision blurred" listed as a secondary preferred term (2003GB00460). This report was confounded by concomitant medications (haloperidol, for which blurred vision has been reported, and procyclidine, for which conjunctivitis and glaucoma have been reported). Scant clinical detail was provided. The patient had not yet recovered from the event at the time of the report.

These reports were confounded by concomitant medications and/or provided insufficient information for clinical analysis. Thus, they do not establish a causal relationship between vision impaired and SEROQUEL and disclosed no new significant safety information about the use of SEROQUEL in children.

Of the two reports of "Conjunctivitis," one report (2004UW11552) described a patient who experienced conjunctivitis after five months of SEROQUEL treatment, which resolved while SEROQUEL was continued, but then reoccurred at a later date. No further information was provided. The other report (2002UW06135) contained scant clinical detail and did not lend itself to analysis.

One additional medically confirmed report had "Conjunctivitis" listed as a secondary preferred term (2000UW00926). This report described a patient who experienced lithium toxicity, NMS, leucopenia, and conjunctivitis. SEROQUEL and loxapine were discontinued and the patient received antibiotic treatment. All events except leucopenia resolved.

Conjunctivitis is usually due to an allergic, inflammatory, or infectious condition involving the eye. It would be unusual for conjunctivitis to be an ADR to a systemically administered drug. Following a review of these reports it was determined that they do not establish a causal relationship between conjunctivitis and SEROQUEL and disclosed no new significant safety information about the use of SEROQUEL in children.

Reports of thyroid and thyroid hormone abnormalities are contained in Table 26 below.

Table 26 Multiple reports for non-serious CDS unlisted topics—Endocrine disorders (10 reports)

Topic	Report	Primary PT	Serious	Secondary PT	Serious
SOC: Endocrine disorders					
Thyroid and thyroid hormone abnormalities (10)	2004UW15552	Thyroid function test abnormal	No	Thyroid disorder	No
	2000UW04134	Thyroid function test abnormal	No	None	NA
	2004UW01066	Hypothyroidism	No	None	NA
	2004UW00198	Hypothyroidism	No	None	NA
	2004AC00329	Hypothyroidism	No	None	NA
	2002UW16548	Hypothyroidism	No	None	NA
	2002UW12497	Hypothyroidism	No	None	NA
	2002UW05579	Hypothyroidism	No	None	NA
	2004UW02108	Blood TSH ↑	No	None	NA
	2003UW03347	Blood TSH ↑	No	None	NA

Summary for thyroid and thyroid hormone abnormalities

Of the 10 reports of thyroid and thyroid hormone abnormalities, one report (2004UW01066; "Hypothyroidism") was confounded by a concomitant medication (oxcarbazepine), for which enhanced thyroid hormone metabolism resulting in reduced serum concentrations of thyroid hormones has been reported. Another report (2000UW04134; "Thyroid function test abnormal") described a patient that experienced fluctuating thyroid stimulating hormone levels. This report was confounded by the patient's medical history of hypothyroidism. Further information was not available for analysis. Another report (2004AC00329; "Hypothyroidism") described a patient who developed hypothyroidism following a minimum of 15 months of SEROQUEL treatment. SEROQUEL was continued, and following two additional months thyroid stimulating hormone values had returned to normal. Further information was not available for analysis.

Another report (2002UW12497; "Hypothyroidism") described a patient who had taken SEROQUEL (100 mg/day) for over two years, and developed hypothyroidism following an increase in dosage (150 mg/day). Information about concomitant medications, whether SEROQUEL was continued, and outcome was not provided. Further information was not available for analysis.

Another report (2004UW15552; "Thyroid function test abnormal") described a patient that experienced abnormal thyroid blood levels and thyroid gland abnormalities after being treated with SEROQUEL for an unknown period of time. SEROQUEL was discontinued and the patient recovered.

Another five reports (2004UW00198; "Hypothyroidism," 2002UW16548; "Hypothyroidism," 2002UW05579; "Hypothyroidism," 2004UW02108; "Blood thyroid stimulating hormone increased," 2003UW03347; "Blood thyroid stimulating hormone increased") contained scant clinical detail and did not lend themselves to analysis.

One additional medically confirmed report had "Hypothyroidism" listed as a secondary preferred term (2003UW05252). The patient experienced hypothyroidism following approximately one year of SEROQUEL treatment. SEROQUEL continued and levothyroxine was added to treat hypothyroidism. Further information including an outcome was not provided.

Of the 11 reports of thyroid and thyroid hormone abnormalities, four were reports of abnormal lab findings only (2004UW15552, 2000UW04134, 2004UW02108, 2003UW03347), and seven were reports of "Hypothyroidism" (2004UW01066, 2004UW00198, 2002UW12497, 2002UW16548, 2002UW05579, 2004AC00329, 2003UW05252). Of the seven reports of "Hypothyroidism," two reports contained laboratory values (2002UW12497, 2004AC00329) and one contained clinical symptoms of hypothyroidism including "huge appetite with no weight gain, flushing, and depression" (2002UW12497). For report 2004AC00329, the event resolved while SEROQUEL continued. For report (2002UW12497), it was not reported if SEROQUEL was continued, and no outcome was provided. Another report (2003UW05252) described a patient who remained on SEROQUEL and initiated treatment with levothyroxine, however, no outcome was provided. The remaining four reports contained scant clinical details and did not lend themselves to analysis (2004UW01066, 2002UW16548, 2004UW00198, 2002UW05579).

The SEROQUEL CDS states:

> "SEROQUEL treatment was associated with small dose-related decreases in thyroid hormone levels, particularly total T_4 and free T_4. The reduction in total and free T_4 was maximal within the first two to four weeks of SEROQUEL treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of SEROQUEL treatment was associated with a reversal of the effects on total and free T_4, irrespective of the duration of treatment. Smaller decreases in total T_3 and reverse T_3 were seen only at higher doses. Levels of TBG were unchanged and in general, reciprocal increases in TSH were not observed, with no indication that SEROQUEL causes clinically relevant hypothyroidism."

These reports were either confounded by concomitant medications or medical history, or provided insufficient information for clinical analysis. Only one of the reports of hypothyroidism included clinical symptoms. Thus, a review of the data did not disclose any significant new safety information about the use of SEROQUEL and decreases in thyroid hormone levels. The data do not establish a causal relationship between clinically relevant hypothyroidism and the use of SEROQUEL in children.

Reports of gastrointestinal disorders are contained in Table 27 below.

Table 27 Multiple reports for non-serious CDS unlisted topic: Gastrointestinal disorders (8 reports)

Topic	Report	Primary PT	Serious	Secondary PT	Serious
SOC: Gastrointestinal disorders					
Vomiting (2)	2004UW01603	Vomiting	No	Feeling hot Rigors Mood swings	No No No
	2004SE04136	Vomiting	No	Nausea Malaise Dizziness	No No No
Nausea (4)	2000UW04213	Nausea	No	Vomiting	No
	2004SE00088	Nausea	No	Vomiting	No
	2003SE04649[a]	Nausea	Yes	Weight ↑ Sedation	Yes Yes
	2002AP01223	Nausea	No	Vomiting	No
Abdominal pain (2)	1997UW43283	Abdominal pain	No	Vomiting	No
	2003UW05498	Abdominal pain	No	Nausea Hyperhidrosis	No No

[a] see section 6.5 for further discussion of this report.

Summary for gastrointestinal disorders

Of the two reports of "Vomiting," one report (2004UW01603) was confounded by a concomitant medication (venlafaxine), for which nausea and vomiting have been reported. In addition, this report was confounded by the patient's current medical status, which included influenza-like symptoms. The other report (2004SE04136; also AE of "Nausea") described a patient who experienced vomiting, nausea, malaise, and dizziness following a rapid downward titration in SEROQUEL dosage (from 600 to 0 mg/day in four days). The patient recovered without sequelae 11 days later and the physician suspected that these were possible withdrawal symptoms. No concomitant medications, medical history, or other information was available.

Four additional medically confirmed reports had "Vomiting" listed as a secondary preferred term (2004SE04540, 2000AP01571, 2004UW18178, 2000UW03450). Two reports (2004UW18178, 2000UW03450) are discussed below for nausea. Another report (2004SE04540) described a patient who experienced the event a day after stopping SEROQUEL. He recovered and no further information was provided. The fourth report (2000AP01571) described a patient who had received SEROQUEL for six days when the event occurred. His medication was changed to amisulpiride, and he recovered. No further information was provided.

Of the four reports of "Nausea," one report (2000UW04213; also AE of "Vomiting") was confounded by a concomitant medication (lithium) for which nausea and vomiting have been reported. Another report (2002AP01223; also AE of "Vomiting) described a patient who experienced nausea following three weeks of SEROQUEL. SEROQUEL was withdrawn and the patient recovered. No further information was available. Another report of "Nausea" (2004SE00088; also AE of "Vomiting) described a patient who experienced nausea and vomiting following four months of SEROQUEL and a recent increase to an 800 mg/day. The patient chose to discontinue SEROQUEL. No further information was provided. The last report (2003SE04649) described a patient who experienced nausea, weight gain and sedation following one week of SEROQUEL. No further information was provided.

Two additional medically confirmed reports had "Nausea" listed as a secondary preferred term (2004UW18178, 2000UW03450). One report (2004UW18178) described a patient who was jailed and abruptly stopped SEROQUEL. No further information was available. The second report (2000UW03450) was confounded by the patient's concomitant medication venlafaxine (for which abdominal pain and vomiting have been reported).

Of the two reports of "Abdominal pain," one report (1997UW43283; also AE of "Vomiting) described a patient who experienced abdominal pain following an unknown time on SEROQUEL. SEROQUEL was discontinued and the patient recovered. The other report (2003UW05498; also AE of "Nausea) contained scant clinical detail and did not lend itself to analysis.

Two additional medically confirmed reports had "Abdominal pain" listed as a secondary preferred term (2003UW12724, 2002UW05916). One report (2003UW12724) described a 16-year-old female living in a detention center, who received SEROQUEL for two nights and was hospitalized two weeks later with hepatic and abdominal pain, hepatic enzyme increased, constipation, and impacted bowels. At the time of the report, she had not yet recovered.

For details of the second report (2002UW05916) see section 6.2 *Topics of interest; Glucose dysregulation.* The report was confounded by concomitant medications including citalopram, for which gastrointestinal disturbances such as nausea, vomiting, dyspepsia, constipation, and diarrhea have been reported; desmopressin, for which mild abdominal cramps have been reported; oxybutynin, for which nausea and vomiting have been reported; and salbuterol, for which muscle cramps, nausea, vomiting, and hyperglycemia have been reported.

These reports were confounded by concomitant medications or medical history, or provided insufficient information for clinical analysis. Following a review of the data, it was determined that the data do not establish a causal relationship between these gastrointestinal disorders and SEROQUEL.

Reports of general disorders are contained in Table 28 below.

Table 28 Multiple reports for non-serious CDS unlisted topic—General disorders (16 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: General disorders and administration site conditions					
Drug ineffective (6)	2004UW14397	Drug ineffective	No	None	NA
	2003UW14599	Drug ineffective	No	Thinking abnormal	No
	2003UW00684	Drug ineffective	No	Heart rate ↑	No
	2002UW11635	Drug ineffective	No	None	NA
	2002UW00575	Drug ineffective	No	None	NA
	2001UW00878	Drug ineffective	No	None	NA
Drug interaction (6)	2004AP03992	Drug interaction	Yes	Depressed level of consciousness	Yes
	2004AC00232[a]	Drug interaction	No	Extrapyramidal disorder Akathisia Parkinsonism Weight ↑	No No No No
	2003UW16449	Drug interaction	No	Tachycardia Chest pain Blood pressure ↑	No No No
	2000UW00479	Drug interaction	No	Antidepressant drug level ↑	No
	2004UW02187	Drug screen positive	No	None	NA
	2004UW20549	Drug screen positive	No	None	NA
Pyrexia (2)	2003UW16728[a]	Pyrexia	Yes	Pharyngolaryngeal pain Salivary hypersecretion Musculoskeletal stiffness Dizziness Dystonia Nuchal rigidity Swollen tongue Streptococcal infection	Yes Yes Yes Yes Yes Yes No No
	1998UW48733	Pyrexia	No	Peripheral ischaemia	No
Temperature regulation disorder (2)	2002UW07129	Temperature regulation disorder	No	None	NA
	2001UW11872	Temperature regulation disorder	No	None	NA

[a] see sections 6.5 and 6.8 for further discussion of these reports, ↑=increased.

Summary for general disorders

Of the six reports of "Drug ineffective," one report (2002UW00575) described a patient who was not responding to treatment with SEROQUEL, possibly because the patient was not complying with medication instruction. No further information was available. Another report (2004UW14397) described a patient who was being treated with SEROQUEL for autism and agitation and found the medication ineffective. There were conflicting subjective reports of drug efficacy among family members. No further information was available. The remaining four reports (2003UW14599, 2003UW00684, 2002UW11635, 2001UW00878) contained scant clinical detail and did not lend themselves to analysis.

Two additional medically confirmed reports had "Drug ineffective" listed as a secondary preferred term (2004GB00484, 2004UW08995). The first report (2004GB00484) described a patient who started SEROQUEL and experienced moderate erythrocyte sedimentation rate increase and drug ineffective. No further information was provided. The second report (2004UW08995) described a patient with a history of drug abuse, depression, psychosis, prior atypical antipsychotic therapy, and post-traumatic stress disorder. After starting SEROQUEL, the patient complained of glossodynia and continued depression and hallucinations. SEROQUEL was discontinued and olanzapine and escitalopram were started. The patient continued to complain of the same symptoms.

These reports were confounded by non-compliance or conflicting information, or provided insufficient information for clinical analysis. Thus, they do not establish a causal relationship between drug ineffectiveness and SEROQUEL use in children.

Of the four reports of "Drug interaction," one report (2004AP03992) described a patient who experienced impaired consciousness 10 days after starting aripiprazole and an unknown time after starting all other medications. The reporter considered the patient's impaired consciousness due to an interaction between SEROQUEL, aripiprazole, diazepam, lamotrigine, midazolam, and valproate. Aripiprazole alone was discontinued and the event resolved.

Another report (2004AC00232) described a patient who after three months of treatment with paroxetine (for which EPS, akathisia, and parkinsonism have been reported) had improved depression. However, nizatidine was initiated to control weight gain. Four weeks later, the patient's weight was reduced and nizatidine was increased. Four days later, the patient experienced EPS. Nizatidine was decreased and the patient recovered. The report author indicated a potential drug interaction between SEROQUEL and nizatidine. The EPS could simply have been due to paroxetine.

Another report (2003UW16449) described a patient who experienced a possible interaction between SEROQUEL and fluoxetine after SEROQUEL was "recently" increased (100 to 400-mg/day). Time-to-onset and outcome were unknown, however the patient continued both SEROQUEL and fluoxetine. Another report (2000UW00479) described a patient experiencing a possible drug interaction between SEROQUEL and clomipramine. The investigator noted that when the patient was receiving equal doses of SEROQUEL and

clomipramine, the patient's clomipramine blood level was normal. When SEROQUEL was increased, but clomipramine remained the same, the clomipramine blood level increased "dramatically." This patient was also taking luvox and inositol. No further information was provided.

Four additional medically confirmed reports had "Drug interaction" listed as a secondary preferred term (2004UW18692, 2002UW00790, 1998UW47387, 2002UW04875). One serious report (2004UW18692) described a patient who mistakenly took three doses of SEROQUEL in one day, for a total of 900 mg. The following day the patient took a prescribed dose of erythromycin and experienced tachycardia, depressed level of consciousness, hypotension, and drug interaction. The patient was hospitalized for observation and recovered. Another report (2002UW00790) described a patient who had been receiving SEROQUEL for a year. After topiramate was started, the patient experienced an increase in liver enzymes. SEROQUEL was reduced and after several days the liver enzymes returned to normal. However, the patient's psychosis grew worse on the lower dose of SEROQUEL. No further information was provided.

Anther report (1998UW47387) described a patient who experienced gastrointestinal distress, paresthesia, sedation, and physical aches following a recent increase in SEROQUEL dosage (200 mg/day). The patient had been treated extensively with fluoxetine prior to and during SEROQUEL treatment and the physician considered these events symptoms of drug interaction. SEROQUEL was continued. Further information was not provided. The final report (2002UW04875) described a patient who experienced increased serum valproate levels immediately (1 day) following an increase in SEROQUEL dosage (50 to 100 mg/day). SEROQUEL continued and valproate was reduced. No further information was provided.

Of the two reports of "Drug screen positive," one report (2004UW02187) described a patient who tested positive for benzodiazepine. Concomitant medications included minocycline and sulfa/trimethroprin. SEROQUEL was continued. No further information was provided. The other report (2004UW20549) contained scant clinical detail and did not lend itself to analysis.

These reports of drug interaction and drug screen positive demonstrated no consistent pattern(s) for any of the possible interacting drugs. For most of these reports information was not provided to confirm altered blood levels, effects on metabolism, or excretion of reported interacting drugs. Some of the reports were confounded with concomitant medications. In view of the incomplete nature of these reports an actual drug interaction or drug screen positive cannot be ascertained.

Of the two report of "Pyrexia," one report (2003UW16728) was confounded by the patient's current medical history of streptococcal infection. The other report (1998UW48733) was confounded by a concomitant medication (valproate), for which increased body temperature has been reported.

Five additional medically confirmed reports had "Pyrexia" listed as a secondary preferred term (2003GB02730, 2002UW17056, 2003AP03768, 2002AP02291, 2003UW14113). One report (2003GB02730) was confounded by a concomitant medication (olanzapine) for which

fever has been reported. Another report (2002UW17056) was confounded by a concomitant medication (bupropion), for which fever has been reported. Another report (2003AP03768) was confounded by concomitant medications (risperidone, for which body temperature dysregulation has been reported, and fluvoxamine, for which increased body temperature has been reported). Another report (2002AP02291) was confounded by concomitant medications carbamazepine, zuclopenthixol, and benzatropine, for all of which fever has been reported. The final report (2003UW14113) was confounded by a concomitant medication (paroxetine), for which increased body temperature has been reported.

Of the two reports of "Temperature regulation disorder," both reports (2002UW07129, 2001UW11872) contained scant clinical detail and did not lend themselves to analysis.

These reports were confounded by concomitant medical conditions or provided insufficient information for clinical analysis. Thus, they do not establish a causal relationship between fever and temperature regulation disorder and SEROQUEL use in children.

Reports of musculoskeletal disorders are contained in Table 29 below.

Table 29 Multiple reports for non-serious CDS unlisted topic—Musculoskeletal disorders (8 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Musculoskeletal and connective tissue disorders					
Blood CPK ↑(4)	2004UW02636	Blood CPK ↑	No	None	NA
	2004PK01317	Blood CPK ↑	No	None	NA
	2001AP05884[a]	Blood CPK ↑	No	Blood prolactin ↑ Weight increased Blood triglycerides ↑	No No No
	1998UW43591	Blood CPK ↑	No	None	NA
Muscle and joint pain (4)	2004GB00668	Pain in extremity	Yes	Diplegia	Yes
	2002UW13929	Pain in extremity	No	None	NA
	1998UW49353	Arthralgia	No	Oedema peripheral Skin lesion	No No
	1998UW49352	Arthralgia	No	Joint swelling Muscle cramp Oedema peripheral Joint swelling	No No No No

[a] see sections 6.5 and 6.11 for further discussion of this report.

Summary for musculoskeletal disorders

Of the four reports of "Blood creatine phosphokinase increased," one report (2004PK01317) was confounded by the patient's medical history, which included a prior increase in blood creatine phosphokinase (CPK) while the patient was being treated with clozapine. Another

report (1998UW43591) was confounded by a concomitant medication (clozapine) for which increased CPK levels have been reported. Another report (2001AP05884) described a patient who experienced blood CPK increased, blood prolactin increased, weight increased, and blood triglycerides increased. Both SEROQUEL and sulpiride were discontinued and the prolactin and triglyceride levels normalized. No outcome was reported for the weight gain and the increased CPK did not resolve. No further information was provided. Another report (2004UW02636) described a patient who was being switched from clozapine to SEROQUEL and on the fourth day (patient was on 50 mg/day clozapine and 500 mg/day SEROQUEL) the patient's CPK values were continuing to rise. No further information was provided.

One additional medically confirmed report had "Blood creatine phosphokinase increased" listed as a secondary preferred term (2003GB02730). This report contained scant clinical data and did not lend itself to analysis.

Of the four reports of muscle and joint pain, one report (2004GB00668; "Pain in extremity") was confounded by concomitant medications fluoxetine and sertraline, for both of which arthralgia and myalgia have been reported. Another report (1998UW49353; "Arthralgia") was confounded by concomitant medications sertraline and famotidine, for both of which arthralgia and myalgia have been reported. Another report (1998UW49352; "Arthralgia") described a patient who was receiving SEROQUEL for 9 days and developed arthralgia and additional leg cramps and pain. SEROQUEL was discontinued and the patient recovered. The remaining two reports (2002UW13929; "Pain in extremity," 2002AP01777; "Muscle cramp") contained scant clinical detail and did not lend themselves to analysis.

One additional medically confirmed report had "Arthralgia" listed as a secondary preferred term (2004UW08065). This report was confounded by the patient's current medical condition of parvovirus. The patient experienced arthralgias and myalgias approximately two months after starting SEROQUEL. The patient had antinuclear antibodies of 1:160 homogenous patterns, which increased to 1:640 homogenous patterns (recorded at an unspecified time). Approximately five months after starting SEROQUEL, the patient had increased CPK level (from 278 to 305; no units). Further testing identified parvovirus. No further information was available.

These reports were confounded by concomitant medications, medical history, or current medical conditions, or provided insufficient information for clinical analysis. Thus, they do not establish a causal relationship between these musculoskeletal disorders and SEROQUEL use in children.

Reports of nervous system disorders are contained in Table 30 below.

Table 30 Multiple reports for non-serious topic—Nervous system disorders (9 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Nervous system disorders					

Table 30 Multiple reports for non-serious topic—Nervous system disorders (9 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Hypoaesthsia (3)	2003UW11552[a]	Hypoaesthsia	No	Paraesthesia Aggression	No No
	1998UW48588	Hypoaesthsia	No	None	NA
	2003UW09171	Hypoaesthsia	No	None	NA
Paraesthesia (2)	2003UW13155	Paraesthesia	No	None	NA
	2003GB00226	Paraesthesia	No	Dizziness	No
Myoclonus (2)	2001SE06318	Myoclonus	No	None	NA
	2003UW15171	Myoclonus	No	None	NA
Headache (2)	2000UW03966	Headache	No	None	NA
	2000UW03965	Headache	No	None	NA

[a] see section 6.13 for further discussion of this report.

Summary for nervous system disorders

Of the three reports of "Hypoaesthsia," all reports (2003UW11552; also contained AE of "Paraesthesia," 1998UW48588, 2003UW09171) contained scant clinical detail and did not lend themselves to analysis.

Of the two reports of "Paraesthesia," both reports (2003UW13155, 2003GB00226) contained scant clinical detail and did not lend themselves to analysis.

Three additional medically confirmed reports had "Paraesthesia" listed as a secondary preferred term (1998UW47387, 2001UW12881, 2004SE03153). One report (1998UW47387) was confounded by a concomitant medication (fluoxetine) for which nervousness and post-withdrawal paresthesia have been reported. The two remaining reports (2001UW12881, 2004SE03153) contained scant clinical detail and did not lend themselves to clinical analysis. In addition, report 2001UW12881 was confounded by concomitant medications zolmitriptan and diphenhydramine (paresthesia has been reported for both) and report 2004SE03153 was confounded by the patient's history of alcoholism and drug (cannabis) abuse.

Of the two reports of "Myoclonus," both reports (2001SE06318, 2003UW15171) contained scant clinical detail and did not lend themselves to analysis.

Of the two reports of "Headache," one report (2000UW03965) was confounded by a family medical history of headaches. Concomitant medications were not provided for this report. The other report (2000UW03966) contained scant clinical detail and did not lend itself to analysis.

One additional medically confirmed report had "Headache" listed as a secondary preferred term (2000AP03966). The patient had a concurrent viral illness, thus confounding the report.

These reports were confounded by the patient's concomitant medications or concomitant medical condition or family history, or provided insufficient information for analysis. Thus, they do not establish a causal relationship between these nervous system disorders and SEROQUEL and disclosed no significant new safety information about the use of SEROQUEL in children.

Reports of psychiatric disorders are contained in Table 31 below.

Table 31 Multiple reports for non-serious CDS unlisted topic—Psychiatric disorders (32 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Abnormal behavior[a] (4)	2004UW15424[b]	Abnormal behavior	Yes	Blood glucose ↑	No
	2001UW10062	Abnormal behavior	No	Anxiety	No
	2001UW03225	Abnormal behavior	No	None	NA
	1999AP00781	Abnormal behavior	No	Aggression	No
Behavior & socialization disturbances (10)	2004UW17956[a]	Aggression	Yes	Agitation Medication error	Yes Yes
	2002UW08404[a]	Aggression	No	None	NA
	1998UW43600[a]	Aggression	No	None	NA
	2003UW09780[a]	Agitation	No	Insomnia	No
	2003UW09050[a,c]	Agitation	No	Akathisia	No
	2003UW08574[a]	Agitation	No	None	NA
	2003UW00640[a]	Agitation	No	None	NA
	2001UW01851[a]	Agitation	No	None	NA
	2000UW03909	Impulsive behavior	No	ADHD Hallucination, auditory	No No
	2003GB03350[a]	Irritability	No	Somnolence	No
Schizophrenia and psychiatric disorders (9)	2002GB00038	Psychotic disorder	Yes	None	NA
	2001SE04627	Schizophrenia	Yes	None	NA
	2001AP05633[d]	Schizophrenia	No	Weight ↑ Sedation	No No
	2004UW05653	Hallucination	No	None	NA
	2001UW10660	Hallucination	No	None	NA
	2001UW05247	Hallucination	No	None	NA
	2003UW16130	Hallucination, auditory	No	Weight ↑	No

Table 31 Multiple reports for non-serious CDS unlisted topic—Psychiatric disorders (32 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Schizophrenia and psychiatric disorders (9	2002UW10888[d]	Hallucination, auditory	No	Paranoia Cognitive disorder Delusion Weight ↑	No No No No
	1998AP44098	Hallucination, auditory	No	Psychiatric symptom	No
Hyperphagia (2)	2004UW12118[d]	Hyperphagia	No	Weight ↑	No
	2004UW11289[d]	Hyperphagia	No	Weight ↑	No
Sleep disorders (4)	1999AP04948[d]	Sleep disorder	No	Weight ↑	No
	2004UW12874	Insomnia	No	None	NA
	2004UW17824	Hypersomnia	No	None	NA
	2001UW02888	Hypersomnia	No	None	NA
Tic (3)	2003UW06615	Tic	No	None	NA
	2000UW01604	Tic	No	Dysphemia	No
	2000UW00771	Tic	No	None	NA

[a,b,c,d] see sections 6.13, 6.2, 6.8, and 6.5, respectively for further discussion of these reports, ADHD=attention deficit hyperactivity disorder, ↑=increased.

Summary for psychiatric disorders

Abnormal behavior: Of the four reports of "Abnormal behavior" one report (2001UW10062; also contained AE of "Anxiety") was confounded by a medical history of mental retardation and somatization disorder. Another report (2004UW15424) described a patient with a family history of DM who also experienced blood glucose increased. The report was confounded by concomitant medications carbamazepine (for which acute psychotic and paranoid symptoms, phobias, and mood disturbances of cerebellar and oculomotor function have been reported), lorazepam (for which confusion, depression, hostility, aggression, and disinhibition have been reported), buspirone (for which psychotic reactions and mania have been reported), and atomoxetine (for which irritability and emotional lability have been reported).

Another report (2001UW03225) was confounded by the medical history of mental retardation and by a concomitant medication (risperidone) for which anxiety, sexual dysfunction, concentration difficulties, and depression have been reported. Another report (1999AP00781; also contained AE of "Aggression") described a patient with a medical history of schizophrenia and was confounded by the concomitant medications carbamazepine (for which acute psychotic and paranoid symptoms, phobias, and mood disturbances of cerebellar and oculomotor function have been reported), haloperidol (for which delirium, agitation, and

depression have been reported), and sertraline (for which anxiety, hallucinations, agitation, confusion, and suicidal ideation have been reported).

One additional medically confirmed report had "Abnormal behaviour" listed as a secondary preferred term (2004UW03555). This report was confounded by the patient's medical history of mild mental retardation.

These reports were confounded by concomitant medications or medical history, and also provided insufficient information for clinical analysis. Thus, they do not establish a causal relationship between abnormal behavior and SEROQUEL use in children.

Behavior and socialization disturbances: Further information on these reports can be found in Section 6.13 *Topic of interest; Behavioural disturbances.*

These reports were confounded by the patient's concomitant medication, concomitant medical condition, or provided insufficient information for analysis. Thus, they do not establish a causal relationship between aggression, agitation, impulsive behavior, and irritability and SEROQUEL use in children.

Schizophrenia and psychiatric disorders: The one report of "Psychotic disorder" (2002GB00038) described a 13-year-old female patient who was receiving SEROQUEL for the treatment of hallucination. Her behavior deteriorated, she became sexually dis-inhibited and hostile. When the dose of SEROQUEL was increased, she recovered and SEROQUEL continued. For "Psychotic disorder," although the event was reported as the primary preferred term in just one report, one additional medically confirmed report had the event listed as a secondary preferred term (2002UW00790). This report described a patient who was treated successfully for one year with SEROQUEL (800 mg/day). Topiramate was initiated and subsequently the liver enzyme values elevated significantly. SEROQUEL was reduced to 400 mg/day at which point the patient's psychosis worsened. No further information was provided.

Of the two reports of "Schizophrenia," one report (2001SE04627) described a patient who was non-responsive to initial anti-psychotic treatment of haloperidol and risperidone, so these were discontinued and SEROQUEL was initiated (dose not specified). Once SEROQUEL was titrated over eight weeks, the dose was further increased to 600 mg/day and pimozide was added to the regime. A decrease in the negative symptoms was reported, but also an increase in positive symptoms continued. It was suggested that the dose of SEROQUEL might need to be further increased to relieve symptoms. The other report (2001AP05633) described a patient who experienced a remission of their long-term schizophrenia while receiving SEROQUEL. This patient experienced an initial weight gain of seven kilograms, but then lost the seven kilograms without dieting while SEROQUEL continued.

Of the three reports of "Hallucination," one report (2004UW05653) was confounded by a concomitant medication (olanzapine) for which delirium and agitation have been reported and by a medical history of depression. Another report (2001UW10660) was confounded by a concomitant medication (methylphenidate) for which aggressive behavior, hallucinations, and

delirium have been reported. This report provided scant clinical detail. The third report (2001UW05247) was confounded by a concomitant medication (propanolol) for which hallucinations, confusion, and sleep disturbances have been reported. This report provided scant clinical detail.

Of the three reports of "Hallucination, auditory," one report (2003UW16130) was confounded by a concomitant medication (escitalopram) for which hallucinations have been reported. The report also provided scant clinical detail. Another report (2002UW10888; also contained AEs of paranoia, cognitive disorder, and delusion) was confounded by a concomitant medication (sertraline) for which hallucinations have been reported). No information was provided on the continuation of therapy or the outcome. Another report (1998AP44098) was confounded by concomitant medications (paroxetine for which hallucination has been reported, and chlorpromazine for which delirium has been reported).

Two additional medically confirmed reports had "Hallucination" listed as a secondary preferred term (2004UW08995, 2004AC00231). One report (2004UW08995) was confounded by the patient's medical history of hallucination. The patient was receiving SEROQUEL for the treatment of depression and hallucination. The second report (2004AC00231) described a patient who overdosed on her mother's SEROQUEL tablets and was confounded by the patient's medical history of bipolar disorder. No further information was available for additional analysis.

These reports either contained events which are part of the disease process of the disease being treated, or were confounded by concomitant medications or provided insufficient information for clinical analysis. They do not establish a causal relationship between psychosis, schizophrenia, and hallucinations and the use of SEROQUEL in children.

Hyperphagia: The two reports of "Hyperphagia," both reports (2004UW12118 and 2004UW11289) contained scant clinical detail and thus did not lend themselves to analysis. Thus, they do not establish a causal relationship between hyperphagia and SEROQUEL use in children.

Sleep disorders: The four reports of sleep disorders, all four reports (1999AP04948; "Sleep disorder," 2004UW12874; "Insomnia," 2004UW17824; "Hypersonic," 2001UW02888; "Hypersonic") contained scant clinical detail. In addition, one of these four reports (2004UW12874) was confounded by a concomitant medication (clonidine) for which trouble sleeping has been reported.

Two additional medically confirmed reports had "Insomnia" listed as a secondary preferred term (2002UW09622, 2000UW00205). One report (2002UW09622) contained scant clinical data and did not lend itself to analysis. The second report (2000UW00205) was confounded by a concomitant medication (topiramate) for which insomnia has been reported.

Two additional medically confirmed reports had "Hypersonic" listed as a secondary preferred term (2003AP04059, 2001UW10775). One report (2003AP04059) was confounded by concomitant medications (valproate, for which sedation and lethargy have been reported, and

sertraline, for which fatigue and drowsiness have been reported). The other report (2001UW10775) described a patient who fainted 20 to 30 minutes after taking one dose (25 mg) of SEROQUEL. The patient recovered after sleeping 18 hours. Blood pressure measurements were not provided.

These reports were confounded by the patient's concomitant medications or provided insufficient information for analysis. Thus, they do not establish a causal relationship between insomnia; hypersonic and other sleep disorders and SEROQUEL use in children.

Tic: Of the three reports of "Tic," one report (2000UW00771) described a teenager who had a tic and was confounded by other "unspecified medications" (that the physician stated could account for the tic). This report contained scant information and did not lend itself to analysis. The second report (2003UW06615) described a 15-year-old female patient who developed a tic when SEROQUEL was increased to 1200 mg daily. This report was confounded by a concomitant medication (carbamazepine) for which the appearance and worsening of tics has been reported. SEROQUEL continued and the outcome was unknown. The third report (2000UW01604; also contained AE of dysphemia) described a 17-year-old male patient who developed motor tics and verbal tics, which included clicking noises, whistling and twitching of his upper extremities when SEROQUEL was increased to 400 mg daily. Events improved when SEROQUEL was decreased to 200 mg daily. Over three months the symptoms recurred when SEROQUEL dose was greater than 150 mg daily and abated when the dose was reduced to 150 mg daily. The patient was treated with clonidine and was considered recovered when maintained on SEROQUEL 100-150 mg daily. Since tics can vary in severity overtime, and can have exacerbations and remissions, it is possible the observed fluctuations in this case may simply be coincidental to the change in SEROQUEL dose.

For "Tic," although the event was reported as the primary preferred term in three reports, one additional medically confirmed report had the event listed as a secondary preferred term (2003UW11938). This report described a patient who had recently been switched from risperidone treatment to SEROQUEL (50 mg/day) for the treatment of autism. The patient developed buccoglossal syndrome and facial tics. SEROQUEL was discontinued and the patient resumed risperidone treatment and recovered. No further information was available for additional analysis. The onset of symptoms following discontinuation of risperidone raised the possibility of a withdrawal symptom to risperidone.

These reports are either confounded by concomitant medications, provide insufficient information for analysis, or may represent the natural course of variability for tics. Thus, they do not establish a causal relationship between tic and the use of SEROQUEL in children.

Reports of urinary incontinence and retention are contained in Table 32 below.

Table 32 Multiple reports for non-serious CDS unlisted topic—Urinary incontinence and retention (6 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Renal and urinary disorders					
Urinary incontinence and retention (6)	2003UW04114	Urinary incontinence	No	None	NA
	2002UW12961	Urinary incontinence	No	None	NA
	2004UW18178	Urinary retention	No	Nausea Vomiting	No No
	2000UW04745	Urinary retention	No	None	NA
	1999UW02629	Urinary retention	No	None	NA
	2002AP02840	Incontinence	No	None	NA

Summary for urinary incontinence and retention

Of the two reports of "Urinary incontinence," one report (2003UW04114) was confounded by a concomitant medication (guanfacine) for which urinary retention and incontinence have been reported. The other two reports (2002UW12961 and 2004UW18178) contained scant detail and did not lend themselves to analysis. One report of "Incontinence" (unspecified) (2002AP02840) provided scant clinical detail and did not lend itself to analysis.

Of the three reports of "Urinary retention," one report (2000UW04745) described a patient who developed urinary retention within two days of starting SEROQUEL. SEROQUEL dosage was decreased twice and each time symptoms improved for one day and then returned. Further information was not provided. Another report (1999UW02629) was confounded by a history of this problem with other antipsychotic medications. Further information was not available for additional analysis. The last report (2004UW18178) contained scant clinical detail and did not lend itself to analysis.

One additional medically confirmed report had "Incontinence" listed as a secondary preferred term (2004UW04388). This report described a patient who experienced psychomotor hyperactivity during treatment with SEROQUEL so SEROQUEL was gradually withdrawn. Subsequently, the patient experienced insomnia and was prescribed escitalopram (for which urinary retention has been reported) and nefazodone. The patient then experienced seizures and was hospitalized. Treatment with diphenhydramine yielded slight improvement. The patient's condition then declined and included hypertonia and incontinence. Further information was not provided for additional analysis.

These reports were confounded by concomitant medications or provided insufficient information for clinical analysis. Thus, they do not establish a causal relationship between urinary incontinence and urinary retention in children using SEROQUEL.

Reports of reproductive and breast disorders are contained in Table 33 below.

Table 33 Multiple reports for non-serious CDS unlisted topic—Reproductive and breast disorders (38 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Reproductive system and breast disorders					
Hyper-prolactinaemia and related disorders[a] (28)	1998AP46145	Amenorrhoea	No	None	NA
	2001UW14772	Amenorrhoea	No	Blood prolactin ↑	No
	2002UW06418	Blood prolactin ↑	No	None	NA
	2003GB00748	Blood prolactin ↑	No	None	NA
	2004UW02051	Blood prolactin ↑	No	None	NA
	2003UW11076	Hyperprolactinaemia	No	None	NA
	2003SE02712	Hyperprolactinaemia	Yes	Breast pain	Yes
	2003GB02687	Hyperprolactinaemia	Yes	None	NA
	2002UW05722	Hyperprolactinaemia	No	None	NA
	2002GB02051	Hyperprolactinaemia	Yes	None	NA
	2000UW00527	Galactorrhoea	No	None	NA
	2001GB00216	Galactorrhoea	No	None	NA
	2002AP01918	Galactorrhoea	No	None	NA
	2003SE03267	Galactorrhoea	No	None	NA
	2003UW07731	Galactorrhoea	No	None	NA
	2003UW13356	Galactorrhoea	No	None	NA
	2003UW13928	Galactorrhoea	No	None	NA
	2004UW18591	Galactorrhoea	No	None	NA
	2002GB00510	Gynaecomastia	No	None	NA
	2002SE04469	Gynaecomastia	No	Hyperthyroidism	No
	2002UW10092	Gynaecomastia	No	None	NA
	2003UW12830	Gynaecomastia	No	None	NA
	2004UW16917	Gynaecomastia	No	None	NA
	2002UW10093	Breast swelling	No	None	NA
	2001UW12390	Breast discharge	No	None	NA
	2002UW13388	Blood testosterone ↓	No	None	NA
	2003UW05543	Erectile dysfunction	No	None	NA
	2002GB02982	Libido ↑	No	None	NA
Other breast disorders (6)	2002AP02404	Breast pain	Yes	Breast abscess	Yes
	2003UW14732	Breast tenderness	No	Vaginal discharge	No
	2004SE04817	Breast discomfort	No	None	NA

Table 33 Multiple reports for non-serious CDS unlisted topic—Reproductive and breast disorders (38 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Other breast disorders (6)	2001AP05465	Breast mass	No	None	NA
	2000UW01303	Breast hyperplasia	No	None	NA
	2004UW10926	Hypertrophy breast	No	None	NA
Menstruation irregularities (4)	2002UW10100	Menorrhagia	No	None	NA
	2000UW03886	Metrorrhagia	No	None	NA
	2002UW11004	Uterine haemorrhage	No	None	NA
	2001UW14054	Dysmenorrhoea	No	None	NA

[a] see section 6.11 for further discussion of these reports, ↑=increased, ↓=decreased.

Summary for reproductive and breast disorders

Prolactinemia and related disorders: For further discussion of these reports, see section 6.11 *Topic of interest; Hyperprolactinemai **and associated adverse events.***

Other breast disorders: Of the six reports of other breast disorders, three reports (2004SE04817 "Breast discomfort," 2000UW01303 "Breast hyperplasia," and 2004UW10926 "Hypertrophy breast") provided scant clinical detail and did not lend themselves to analysis. Another of the six reports (2002AP02404; "Breast pain" and "Breast abscess") indicated that the 18-year-old female patient was receiving SEROQUEL (dose unknown) for 32 days when the AEs began and continued treatment as the AEs were resolving. Blood prolactin levels were within normal range during the recovery. Another report (2003UW14732; "Breast tenderness") described an obese 15-year-old patient who was receiving SEROQUEL. No outcome was provided. Potentially confounding medications included oxicarbazepine (for which male infertility, gynaecomastia, and galactorrhoea have been reported). The last report (2001AP05465; "Breast mass") described an 18-year-old male patient who was receiving SEROQUEL for a few weeks before onset. SEROQUEL was discontinued, however no outcome was reported. Potentially confounding medications included flunitrazepam (for which galactorrhoea, gynaecomastia, and increased plasma-testosterone concentrations have been reported).

One additional medically confirmed report had "Breast pain" listed as a secondary preferred term (2003SE02712). This report described a patient who experienced hyperprolactinemia and breast pain following 2.5 months of SEROQUEL. SEROQUEL continued and the patient had not yet recovered. No further information provided. For more details regarding this report see section 6.11 *Topics of interest*; *Hyperprolactinemia and related adverse events.*

These reports were confounded by the patient's concomitant medication or provided insufficient information for analysis. Thus, they do not establish a causal relationship between reproductive and breast disorders and SEROQUEL and disclosed no significant new safety information about the use of SEROQUEL.

Menstruation irregularities: Of the four reports of menstruation irregularities, three reports (2000UW03886 "Metrorrhagia," 2001UW14054 "Dysmenorrhoea," 2002UW11004; "Uterine haemorrhage") provided scant clinical detail and did not lend themselves to analysis. Another report (2002UW10100; "Menorrhagia") described a patient who received SEROQUEL for over one year prior to the AE. Treatment changes and outcome were not reported. Potentially confounding medications included fluvoxamine (for which hyperprolactinaemia and galactorrhoea have been reported).

These reports were potentially confounded by concomitant medications or provided insufficient information for clinical analysis. They did not establish a causal relationship between reproductive and breast disorders and SEROQUEL and disclosed no significant new safety information about the use of SEROQUEL.

Reports of epistaxis are contained in Table 34 below.

Table 34 Multiple reports for non-serious CDS unlisted topic—Epistaxis (4 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Blood and lymphatic system disorders					
Epistaxis (4)	2001AP00216	Epistaxis	No	None	NA
	2000AP03966	Epistaxis	No	LFT abnormal Headache Lymphocytosis	No No No
	2000AP03965	Epistaxis	No	None	NA
	2000AP03964	Epistaxis	No	None	NA

LFT=liver function test.

Summary for epistaxis: Of the four reports of "Epistaxis," two reports (2000AP03965, 2000AP03964) contained scant clinical detail and did not lend themselves to analysis. Another report (2000AP03966) was also scant, but it noted the patient had a concurrent viral illness. Another report (2001AP00216) described a patient who experienced epistaxis four days after starting SEROQUEL and four days after stopping haloperidol and levomepromazine. The epistaxis resolved the same day, while SEROQUEL treatment continued.

These reports provided insufficient information for clinical analysis or described the event resolving while SEROQUEL continued. Thus, they do not establish a causal relationship between epistaxis and the use of SEROQUEL in children.

Reports of skin disorders are contained in Table 35 below.

Table 35 Multiple reports for non-serious topic—Skin disorders (29 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Rash (13)	2004UW17212	Rash	No	None	NA
	2003UW05857	Rash	No	None	NA
	2002UW03556	Rash	No	None	NA
	2002UW11896	Rash	No	None	NA
	2001UW04989	Rash	No	Pruritis	No
	2001UW00147	Rash	Unk	None	NA
	1998UW49438	Rash	No	None	NA
	2002UW04858	Rash maculopapular	No	None	NA
	2000UW01055	Rash maculopapular	No	None	NA
	1998UW48100	Rash maculopapular	No	None	NA
	2003UW08431	Rash macular	No	None	NA
	2004UW01819	Rash generalised	No	Rash pruritic	No
	2004UW00834	Rash generalised	No	Pruritis	No
Skin discoloration (3)	2003UW09551	Skin discolouration	No	None	NA
	2002UW01382	Skin discolouration	No	None	NA
	1999UW02462	Skin discolouration	No	None	NA
Face oedema (2)	2004AC00203	Face oedema	No	Eyelid oedema	No
	2003UW02076	Face oedema	No	None	NA
Hyperhidrosis (3)	2003UW14113[a]	Hyperhidrosis	Yes	Somnolence Pyrexia Serotonin syndrome Tachycardia Muscle twitching Loss of consciousness	Yes Yes Yes Yes Yes Yes
	2003GB02730	Hyperhidrosis	No	Blood CPK ↑ Pyrexia Tachycardia	No No No
	2002UW09622	Hyperhidrosis	No	Insomnia	No
Alopecia (6)	2004UW08766	Alopecia	No	None	NA
	2004UW06250	Alopecia	No	None	NA
	2002UW07798	Alopecia	No	None	NA
	2001UW00870	Alopecia	No	None	NA
	2000UW03532	Alopecia	No	None	NA
	1999UW01925	Alopecia	Not provided	None	NA

Table 35 Multiple reports for non-serious topic—Skin disorders (29 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Blister (2)	2001SE06271	Lip blister	No	None	NA
	2002UW16830	Blister	Yes	None	NA

[a] see section 6.8 for further discussion of this report, CPK=creatine phosphokinase.

Summary for skin and subcutaneous tissue disorder

Face oedema, skin discoloration, and hyperhydrosis: Of the three reports of "Skin discoloration," one report (2002UW01382) was confounded by a concomitant medication (carbamazepine) for which photosensitivity and hypersensitivity reactions have been reported. Another report (2003UW09551) was confounded by concomitant medications (fusidic acid, for which skin rash and irritation have been reported, terbutaline, for which hypersensitivity reactions have been reported, and acetaminophen, for which hypersensitivity reactions have been reported). In addition, this report is confounded by the patient's medical history of drug hypersensitivity. Another report (1999UW02462) described a patient who developed darkening of the pigment around the knuckles, knees and elbows following an unknown length of time on SEROQUEL. No further information was provided.

Of the two reports of "Face oedema," one report (2004AC00203) was confounded by a concomitant medication (valproate) for which oedema has been reported. Another report (2003UW02076) contained scant clinical detail and did not lend itself to analysis. For "Face edaema," although the event was reported as the primary preferred term in just two reports, one additional non-serious medically confirmed report had the event listed as a secondary preferred term (2001UW14363). Details about the face edema and outcome were not reported.

Of the three reports of "Hyperhydrosis," one report (2003UW14113) was confounded by concomitant medications (paroxetine, for which hyperhidrosis has been reported, and lactated ringer's solution, for which sweating has been reported). The remaining two reports (2003GB02730, 2002UW09622) contained scant clinical detail and did not lend themselves to analysis.

Four additional medically confirmed reports had "Hyperhidrosis" listed as a secondary preferred term (2001UW07886, 2003UW05498, 2002UW12005, 1998AP46653). Two of these reports (2001UW07886, 2003UW05498) contained scant clinical detail and did not lend themselves to analysis. Another report (2002UW12005) was confounded by concomitant medications (risperidone, for which impaired body temperature regulation has been reported, pantoprazole, for which sweating has been reported, paroxetine, for which increased body temperature and excessive sweating has been reported, and buspirone, for which sweating has been reported). SEROQUEL was discontinued and the patient recovered. The fourth report (1998AP46653) was confounded by concomitant medications (sertraline, for which excessive sweating has been reported, and clozapine, for which impaired body temperature regulation has been reported).

Of the 13 reports of rash, one report (2004UW01819; "Rash generalized") was confounded by a concomitant medication (metoprolol) for which rash has been reported. Another report (2004UW00834; "Rash generalized") was confounded by a concomitant medication (escitalopram) for which pruritus, skin rash, and urticaria have been reported. Another report (2002UW11896; "Rash") was confounded by a concomitant medication (venlafaxine) for which pruritus and skin rash have been reported. Another report (2002UW04858; "Rash maculo-papular") was confounded by a concomitant medication (venlafaxine) for which pruritus and skin rash have been reported. Another report (1998UW48100; "Rash maculo-papular") was confounded by concomitant medications (loxapine for which hypersensitivity reactions including urticaria, exfoliative dermatitis, erythema multiforme, and contact sensitivity have been reported, carbamazepine for which urticaria, exfoliative dermatitis, and erythema multiforme have been reported, risperidone for which urticaria, exfoliative dermatitis, erythema multiforme, and rash have been reported, and venlafaxine and benztropine for both of which skin rash have been reported). Another report (2000UW01055; "Rash maculo-papular") described a patient who experienced a raised maculo-papular rash on the backs of the hands and on the cheeks following two to four weeks of SEROQUEL treatment. Medical history, concomitant medications, treatment, and outcome were not provided. Another report (2001UW00147; "Rash") described a patient who developed a rash on the extremities on the second day of SEROQUEL therapy. No further information was provided. Another report (2004UW17212; "Rash") described a patient who developed a rash after taking the first dose of SEROQUEL. The patient was treated with diphenhydramine and recovered within 36 hours. The patient's medication was changed to olanzapine. The remaining five reports (2003UW08431; "Rash macular," 1998UW49438; "Rash," 2001UW04989; "Rash," 2002UW03556; "Rash," 2003UW05857; "Rash") contained scant clinical detail and did not lend themselves to analysis.

Three additional medically confirmed reports had "Rash" listed as a secondary preferred term (2003UW02493, 2002AP02291, 2003UW02945). One of these reports (2003UW02493) was confounded by the patient's medical history of viral meningitis. No further information was available for additional analysis. Another report (2002AP02291) was confounded by concomitant medications (benzatropine and carbamazepine, for both of which rash has been reported, and zuclopenthixol, for which hypersensitivity reactions including urticaria, exfoliative dermatitis, and erythema multiforme have been reported). The third report (2003UW02945) described a patient who overdosed on SEROQUEL and experienced a rash. The hospital pharmacist reported that the rash was not due to SEROQUEL use. No further information was provided. For "Rash maculopapular," although the event was reported as the primary preferred term in three reports, one additional medically confirmed report had the event listed as a secondary preferred term (2000AP02801). This report was confounded by the patient's medical history of drug hypersensitivity. SEROQUEL was discontinued and the patient recovered.

These reports were confounded by concomitant medications or provided insufficient information for clinical analysis, or they appeared to describe a hypersensitivity reaction. Hypersensitivity is a listed event in section 4.8 *Undesirable effects* section of the SEROQUEL CDS as an uncommon (≥ 0.1 to <1%). Thus, this data disclosed no significant new safety

information about the use of SEROQUEL in children and rash, skin discoloration, hyperhydrosis, and face edema.

Alopecia: Of the six reports of "Alopecia," one report (2004UW08766) was confounded by two concomitant medications (progesterone and citalopram) for which alopecia has been reported. Another two reports (2004UW06250 and 2002UW07798) were confounded by a concomitant medication (citalopram) for which alopecia has been reported. Another report (2000UW03532) was confounded by a concomitant medication (sertraline) for which alopecia has been reported. Another report (2001UW00870) described a patient who developed loss of pubic and body hair within two weeks of starting SEROQUEL. SEROQUEL was continued, but no outcome was provided. Another report (1999UW01925) described a patient who experienced hair loss four days after starting SEROQUEL. Medical history was unknown. SEROQUEL continued but the patient had not yet recovered.

These reports were confounded by concomitant medications or provided insufficient information for clinical analysis. Thus, they do not establish a causal relationship between alopecia and SEROQUEL and disclosed no significant new safety information about the use of SEROQUEL in children.

Blister: Of the two reports of blister, one report (2001SE06271; "Lip blister") was confounded by a concomitant medication (pantoprazole) for which skin reactions (most were non-specific rashes, pruritus, urticaria, erythematous rashes, and photosensitive eruptions) have been reported. Another report (2002UW16830; "Blister") described a patient who was taking SEROQUEL (100 mg/day, duration unknown) for an unspecified condition. The patient experienced blisters all over the body, predominately around the face and eye. The patient was hospitalized and the outcome was unknown. No further information was provided.

These reports were confounded by concomitant medications or provided insufficient information for clinical analysis. Thus, they do not establish a causal relationship between blister and SEROQUEL use in children and disclosed no significant new safety information about the use of SEROQUEL.

Reports of hot flush are contained in Table 36 below.

Table 36 Multiple reports for non-serious CDS unlisted topic—Hot flush (2 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Vascular disorders					
Hot flush (2)	2002UW12005	Hot flush	Yes	Delirium	Yes
				Hyperhidrosis	Yes
	1998AP46653	Hot flush	No	Hyperhidrosis	No

Summary for hot flush: Of the two reports of "Hot flush," one report (2002UW12005) was confounded by concomitant medications (risperidone for which impaired body temperature regulation has been reported, pantoprazole for which sweating has been reported, paroxetine for which increased body temperature and excessive sweating has been reported, and buspirone for which sweating has been reported. The other report (1998AP46653) was confounded by concomitant medications (sertraline for which increased body temperature has been reported, and clozapine for which impaired body temperature regulation has been reported).

Both reports of "Hot flush" were confounded by concomitant medications. Thus, they do not establish a causal relationship between hot flash and SEROQUEL and disclosed no significant new safety information about the use of SEROQUEL in children.

Single reports for CDS unlisted topic (81 reports)

All single reports for CDS unlisted topics are contained in Table 37 below.

Table 37 Single report for CDS unlisted topic (81 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Blood and lymphatic system disorders					
Anaemia	2001UW01813	Anaemia	Yes	None	NA
Agranulocytosis	1999UW01989[a]	Agranulocytosis	Yes	Leukopenia	Yes
Neutrophil toxic granulation	2004UW05171	Neutrophil toxic granulation present	Yes	None	NA
Prothrombin time prolonged	2000AP03084	Prothrombin time prolonged	No	None	NA
RBC sedimentation rate ↑	2004GB00484	RBC sedimentation rate ↑	No	Drug ineffective	No
SOC: Endocrine disorders					
Hyperthyroidism	2000UW04803	Hyperthyroidism	No	None	NA
SOC: Eye disorders					
Eyelid	2004UW09749	Eyelid function disorder	No	None	NA
Eye movement	2003UW13268	Eye movement disorder	No	None	NA
Eye pain	2002UW10356	Eye pain	No	Intraocular pressure test	No
Accommodation	2001UW01540	Accommodation disorder	No	None	NA

Table 37 Single report for CDS unlisted topic (81 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Eye irritation	2000UW00237	Eye irritation	No	Photophobia Neurological eyelid disorder	No No
SOC: Gastrointestinal disorders					
Swollen tongue	2004UW09774	Swollen tongue	No	Dysphagia	No
Glossodynia	2004UW08995	Glossodynia	No	Hallucination Depression Drug ineffective	No No No
Glossitis	2001UW06830	Glossitis	No	None	NA
Ileus	2004UW17434	Ileus	Yes	Intestinal dilatation Gastrointestinal motility disorder Irritable bowel syndrome Abdominal distension	No No No No
Flatulence	2004UW16031	Flatulence	No	Hiccups	No
Eructation	2004UW11614	Eructation	No	None	NA
Diarrhoea	2002UW14600	Diarrhoea hemorrhagic	No	None	NA
Faecaloma	2002UW08543	Faecaloma	Yes	Constipation Fecal incontinence	Yes Yes
Gastroesophageal reflux	2001AP00919	Gastroesophageal reflux disease	Yes	Haematemesis Heart rate increased	Yes Yes
Gingivitis	1999UW01718	Gingivitis	No	Gingival swelling	No
Gastrointestinal discomfort	1998UW47387	Gastrointestinal discomfort	No	Paraesthesia Sedation Drug interaction Pain	No No No Not provided
Pancreatitis	2003UW04094	Pancreatitis	Yes	None	NA
Stool analysis abnormal	2001UW05344	Stool analysis abnormal	No	None	NA

Table 37 Single report for CDS unlisted topic (81 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: General disorders					
Gait	2004UW04448	Gait abnormal	No	Fear	No
				Anxiety	No
				Feeling abnormal	No
				Dry mouth	No
				Somnolence	No
Hypothermia[b]	2003SE00244	Hypothermia	Yes	Dizziness	Yes
				Somnolence	Yes
				Akathisia	Yes
				Angioneurotic oedema	Yes
Chest pain	1999UW03677	Chest pain	Not provided	Wheezing	No
				Viral infection	No
Drug withdrawal	2004SE04540	Drug withdrawal syndrome	No	Vomiting	No
				Dizziness	No
Medication error	2001AP01126	Medication error	No	Therapeutic agent toxicity	Yes
SOC: Hepatobiliary disorders					
Jaundice	2004UW05326	Jaundice	No	Blood TSH abnormal	No
				Blood ALP ↑	No
Hepatic pain	2003UW12724	Hepatic pain	No	Dizziness	No
				Hepatic enzyme↑	No
				Constipation	No
				Faecaloma	No
				Abdominal pain	No
				Medication error	No
Blood bilirubin increased	2003UW00519	Blood bilirubin ↑	Yes	Leukocytosis	Yes
				Platelet count ↓	Yes
SOC: Immune system disorder					
	2004UW08065	Antinuclear antibody positive	Yes	Parvovirus infection	No
				Arthralgia	No
				Myalgia	No
				Blood CPK ↑	No
	2002UW16591	Sjogren's syndrome	No	None	NA
SOC: Infections and infestations					
	2000UW04683	Sinusitis	No	Otitis media	No

Table 37 Single report for CDS unlisted topic (81 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
	2003UW14488[c]	Viral infection	No	Weight ↑	No
				Thirst	No
				Pollakiuria	No
				Otitis media	No
				Eye swelling	No
				Eye redness	No
	2002UW17056	Infectious mononucleosis	Yes	Lymphocyte count ↓	Yes
				Neutrophil count↓	Yes
				WBC count ↓	Yes
				LFT abnormal	Yes
				Pyrexia	Yes
	2000AP02801	Influenza like illness	No	Rash maculopapular	No
SOC: Investigations					
	2003UW00724	Weight ↓	No	Hyperthyroidism	No
SOC: Ear disorders					
	2000UW02896	Ear pain	No	None	NA
SOC: Metabolism and nutrition disorders					
	1999AP05792[c]	Increased appetite	No	Weight ↑[c]	No
SOC: Musculoskeletal and connective tissue disorder					
	2002AP01777	Muscle cramp	No	None	NA
SOC: Nervous system disorders					
Aphasia	2001UW15489	Aphasia	No	None	NA
Ataxia	2003UW15394[b]	Ataxia	No	Nuchal rigidity	No
Coma	2002UW10534	Coma	Yes	Drug screen false positive	No
Cranial nerve disorder	2000UW00084	Cranial nerve disorder	No	None	NA
Dysphemia	2002UW06614	Dysphemia	No	Eye movement disorder	No
Facial palsy	2002UW16182	Facial palsy	No	None	NA
Loss of consciousness	2004PK00544	Loss of consciousness	No	Hypotension	No
Meige's syndrome	2002AP02582	Meige's syndrome	Yes	None	NA

Table 37 Single report for CDS unlisted topic (81 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Migraine	2000UW04024	Migraine	No	Diplopia	No
Status epilepticus[d]	2000UW00205[d]	Status epilepticus[d]	Yes	Coma	Yes
				Intracranial pressure ↑	Yes
				Brain oedema	Yes
				Brain herniation	Yes
				Metabolic acidosis	Yes
				Hypokalemia	Yes
				Hepatitis	Yes
				Ammonia ↑	Yes
				Activated partial thromboplastin time prolonged	Yes
				INR increased	Yes
				Body temperature ↑	Yes
				Head banging	Yes
				Insomnia	Yes
				Depression	Yes
				Facial bones fracture	Yes
Lethargy	1999AP04980	Lethargy	No	Somnolence	No
SOC: Psychiatric disorders					
Anxiety	2003UW02259	Anxiety	No	None	NA
Confusional state	2003UW14504	Confusional state	No	None	NA
Crying	2001UW10374	Crying	No	None	NA
Disturbance in attention	2004UW09659	Disturbance in attention	No	Insomnia	No
Eating disorder	2004UW12117	Eating disorder	No	Enuresis	No
				Polyuria	No
Fear	2004UW04394	Fear	No	Anorexia	No
				Gait abnormal	No
				Cognitive disorder	No
				Dry mouth	No
				Anxiety	No
				Sedation	No
Psychomotor hyperactivity[b]	2004UW04388	Psychomotor hyperactivity	No	Insomnia	No
				Convulsion	Yes
				Hypertonia	Yes
				Incontinence	Yes

Table 37 Single report for CDS unlisted topic (81 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Psychosexual disorder	2002SE02811	Psychosexual disorder	No	None	NA
Restlessness	2002UW07087	Restlessness	No	None	NA
SOC: Renal and urinary disorders					
Micturition urgency	2001UW08995	Micturition urgency	No	Urinary incontinence Menorrhagia	No No
Nephritis interstitial	2000UW01688	Nephritis interstitial	Yes	None	NA
Pollakiuria	2002AP02377	Pollakiuria	No	None	NA
Renal haemorrhage	2001UW01663	Renal haemorrhage	Yes	None	NA
Renal impairment	2004UW14134	Renal impairment	No	None	NA
SOC: Reproductive and breast disorders					
Blood oestrogen decreased	2004AP03766	Blood oestrogen decreased	No	None	NA
Blood oestrogen increased	2000UW04270	Blood oestrogen increased	No	None	NA
Epididymitis	2004UW02012	Epididymitis	No	Testicular swelling Testicular pain	No No
SOC: Respiratory, thoracic, and mediastinal disorders					
Dyspnea	2004UW08542	Dyspnoea	No	None	NA
Nasal congestion	2004AP02990	Nasal congestion	No	None	NA
Pharyngolaryngeal pain	2002UW17108	Pharyngolaryngeal pain	No	None	NA
Cough	2002UW16194	Cough	No	None	NA
Throat tightness	2001UW12881	Throat tightness	No	Paraesthesia Dyspnoea Blood pressure↑	No No No
SOC: Skin and subcutaneous disorders					
Acne	2004UW00358	Acne	No	Scrotal ulcer	No
Dry skin	2004GB01173	Dry skin	No	Dyspepsia Nightmare	No No
Erythema nodosum	2002UW03842	Erythema nodosum	No	None	NA
Photosensitivity reaction	2002AP02670	Photosensitivity reaction	No	None	NA

Table 37 Single report for CDS unlisted topic (81 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Vascular disorders					
Peripheral coldness	2000UW03657	Peripheral coldness	No	Speech disorder Bradyphrenia	No No
Circulatory collapse	1998AP46181	Circulatory collapse	Yes	Bradycardia Hypotension Respiratory rate ↓	Yes Yes Yes

[a,b,c,d,m] see sections 6.4, 6.8. 6.5. and 6.15, respectively, for further discussion of these reports.

Summary for single reports for non-serious CDS unlisted topics:

For more details regarding the report 1999UW01989, see section 6.4 *Topics of interest; Agranulocytosis*. For each of the preferred terms listed in Table 37 above, the reports involved a single report for each event (or topic). Therefore, no trends could be identified from these reports.

5.5 Non-medically confirmed reports (116 reports)

5.5.1 Newborns (age 0 to 27 days; 2 reports)

5.5.1.1 CDS listed topics (0 reports)

There were no medically unconfirmed reports for CDS listed topics received for this age group.

5.5.1.2 CDS unlisted topic (2 reports)

Multiple reports for CDS unlisted topics

Reports of neonatal hypotonia are contained in Table 38 below.

Table 38 Multiple reports for serious CDS unlisted topic (2 reports)

Topic	Report	Age /sex	Dose/ TTO	Medical history	Concomitant medications	PTs/Comment
Neonatal hypotonia	2004UW06097 Serious	?/F	Not provided	Not provided	Citalopram, lorazepam, trazodone, zoplicone	PTs: Hypotonia neonatal, Respiratory depression, Eye disorder. Outcome unk. No other info.

Table 38 Multiple reports for serious CDS unlisted topic (2 reports)

Topic	Report	Age /sex	Dose/ TTO	Medical history	Concomitant medications	PTs/Comment
Neonatal hypotonia	2004UW06148 Serious	?/F	Not provided	Not provided	Lorazepam, zoplicone, citalopram, trazodone, methotrimeprazine, perphenazine	PTs: Hypotonia neonatal; Neonatal disorder, Eye disorder Baby w/ hypotonia, unspecified disorder, eye abnormality. Outcome unk

? or unk=unknown, info=information, w/=with.

Summary for neonatal hypotonia

Both of these reports (2004UW06097, 2004UW06148; both also contained the PT "Eye disorder") contained scant clinical detail and did not lend themselves to analysis. No further information was available for these reports.

5.5.2 Infants and toddlers (age 28 days to 23 months; 1 report)

5.5.2.1 CDS listed topics (1 report)

There was one medically unconfirmed report for CDS listed topics in this age group, which is listed in Table 39 below.

Table 39 Single report for CDS listed topic (1 report)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Movement disorder	2004UW00073	Movement disorder	No	Somnolence Drug exposure via breast milk	No No

Summary for movement disorder

This report (2004UW00073) contained scant clinical detail and did not lend itself to analysis. No trends could be identified from the report.

5.5.2.2 CDS unlisted topics (0 reports)

There were no medically unconfirmed reports for CDS unlisted topics received for this age group.

5.5.3 Children (age 2 to 11 years; 36 reports)

5.5.3.1 CDS listed topics (11 reports)

Multiple reports for CDS listed topics

Reports of overdose and EPS are contained in Table 40 below.

Table 40 Multiple reports for CDS listed topic (8 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Injury, poisoning, and procedural complications					
Overdose[a]	2004SE03695	Accidental OD	Yes	Convulsion Medication error	Yes Yes
	2004SE03694	Accidental OD	Yes	Convulsion Medication error	Yes Yes
	2004SE03690	Coma (in the setting of OD)	Yes	Accidental overdose Medication error	Yes Yes
SOC: Nervous system disorders					
Extrapyramidal symptoms[b]	2003UW10352	Extrapyramidal disorder	No	None	NA
	2003UW02049[c]	Dyskinesia	No	Agitation	No
	2003UW16631	Dystonia	Yes	None	NA
	2001UW06548	Psychomotor hyperactivity	No	Early morning awakening Dyskinesia	No No
	2003UW10456	Psychomotor hyperactivity	No	Insomnia	No

[a,b,c] see sections 6.14, 6.8, and 6.13 for a further description of these reports.

Summary for overdose and EPS

One additional medically unconfirmed report contained "Accidental overdose" as a secondary preferred term (2004SE03690). Three reports in Table 40 above each contained the following MedDRA preferred terms as a secondary term: (2001UW06548; "Dyskinesia"), (2000UW01272; "Tremor"), and (2003UW10706; "Muscle twitching").

For an analysis of all these reports of EPS and overdose, see Topics of Interest sections 6.8 *Topics of interest; Extrapyramidal symptoms*, and 6.14 *Overdose*, respectively.

Single report for CDS listed topic

Single reports for CDS listed topics are contained in Table 41 below.

Table 41 Single report for CDS listed topic (3 reports)

Topic	Reports	Primary PT	Serious	Secondary PTs	Serious
SOC: Investigations					

Table 41 Single report for CDS listed topic (3 reports)

Topic	Reports	Primary PT	Serious	Secondary PTs	Serious
Weight gain[a]	2004UW16895	Weight ↑	No	Choking	No
				Vision blurred	No
				Dizziness	No
				Nausea	No
				Musculoskeletal stiffness	No
				Body temperature ↑	No
				Abdominal pain	No
				Constipation	No
				Hemorrhage	No
				Headache	No
				Dry mouth	No
				Heart rate ↑	No
				Hyperhidrosis	No
SOC: Nervous system disorders					
Convulsion	2001UW01318	Convulsion	Yes	Markedly reduced dietary intake	No
				Intestinal functional disorder	No
Somnolence	2003UW14985	Somnolence	No	Mania	No

[a] See section 6.5 for discussion of this report.

Summary for single reports for CDS listed topics:

Two additional medically unconfirmed reports (2004SE03695, 2004SE03694) contained "Convulsion" as a secondary term preferred term. One additional medically unconfirmed report (2002UW03379) contained "Somnolence" as a secondary preferred term. One additional medically unconfirmed report (2000UW01272) contained "Sedation" as a secondary preferred term.

See section 6.5 *Topics of interest; Weight gain* for a further discussion of the report of "Weight gain."

The events contained in Table 41 as well as in the paragraph above are listed in the SEROQUEL CDS for the adult population. Following a review of these reports, it was determined that there was no difference in frequency, severity or characteristics of these events when compared to the known profile of SEROQUEL in adults.

5.5.3.2 CDS unlisted topics (25 reports)

There was no serious CDS unlisted topic for which multiple medically unconfirmed reports were received for this age group.

The multiple reports for non-serious unlisted topics are contained in Table 42 below.

Table 42 Multiple report for non-serious CDS unlisted topic (6 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Nervous system disorders					
Lethargy	2002UW03379	Lethargy	No	Somnolence	No
	2004UW18450	Lethargy	No	Fatigue	No
SOC: Psychiatric disorders					
Behavioural disturbances[a]	1999UW04374	Aggression	No	None	NA
	2002UW06190	Aggression	Yes	Heart rate ↑ Sleep terror Hallucination	Yes Yes Yes
	2001UW14903	Hostility	No	None	NA
	2004UW00979	Agitation	No	Hostility	No

[a] See section 6.13 for discussion of this report.

Summary for lethargy: Of the two reports of lethargy (2002UW03379, 2004UW18450), both contained scant clinical detail and did not lend themselves to analysis.

Summary for behavioural disturbances: For the four reports of behavioural disturbances, see 6.13 *Topic of interest; Behavioral disturbances* for analysis.

Single reports for CDS unlisted topics (19 reports)

Single reports for CDS unlisted topics are contained in Table 43 below.

Table 43 Single report for CDS unlisted topic (19 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Gastrointestinal disorders					
Pancreatitis	2000UW01219	Pancreatitis	No	Cognitive disorder	No
Abdominal pain	2000UW02980	Abdominal pain lower	No	↑ appetite	No
Dysphagia	2004UW18667	Dysphagia	No	None	NA
Fecal incontinence	2001UW14270	Faecal incontinence	No	None	NA
Vomiting	2003UW07614	Vomiting	No	None	NA
SOC: Injury, poisoning, and procedural complications					

Table 43 Single report for CDS unlisted topic (19 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Med error	2000UW01272	Accidental exposure	No	Crying	No
				Sedation	No
				Tremor	No
				Rigors	No
				Pyrexia	No
				Hyperhidrosis	No
				Vomiting	No
				Nervousness	No
SOC: Metabolism and nutrition disorders					
Glucose dysregulation	2004UW19755[a]	Diabetes mellitus	No	Constipation	No
				Abdominal pain upper	No
SOC: Nervous system disorders					
Paralysis	2003UW06070	VI nerve paralysis	Yes	None	NA
Headache	2004UW06135	Headache	No	Intracranial pressure ↑	No
				Vomiting	No
				Insomnia	No
				Visual disturbance	No
Attention	2003UW11338[b]	Disturbance in attention	No	Restlessness	No
				Adjustment disorder	No
				Agitation	No
				Aggression	No
				Drug interaction inhibition	No
Coordination	2004UW04660	Coordination abnormal	No	None	NA
SOC: Psychiatric disorders					
Anxiety	2003UW10706[c]	Anxiety	No	Muscle twitching	No
				Cough	No
Hallucination	2003UW16200	Hallucination	No	None	NA
Mania	2001UW12559	Mania	Yes	Leukopenia	Yes
Miscellaneous reports					
Epistaxis	2003UW02832	Epistaxis	No	None	NA
ECG T wave	2003UW09328	ECG T wave inversion	No	None	NA
Dyspnoea	2004UW16775	Dyspnoea	No	None	NA
Pigmentation	2001UW15471	Pigmentation disorder	No	None	NA
Unexpected effect	2000UW02823	Unexpected therapeutic drug effect	No	None	NA

[a,b,c] see sections 6.2, 6.13, and 6.8, respectively for a further discussion of these reports, ECG=electrocardiogram.

Summary for single reports for CDS unlisted topics

For most of the events reported in Table 43 above (pancreatitis, fecal incontinence, accidental exposure, VI nerve paralysis, disturbance in attention, coordination abnormal, anxiety, epistaxis, ECG T wave inversion, dyspnea, pigmentation disorder, and unexpected therapeutic drug effect), only a single report for each event (or topic) was received. Therefore, no trends could be identified from these reports. For some of the events reported in Table 43 above, additional reports were identified that had the event listed as a secondary preferred term: "Hallucination" (2002UW06190), "Mania" (2003UW14985), "Headache" (2004UW16895), "Abdominal pain upper" (2004UW19755) and "Abdominal pain" (2004UW16895), and "Vomiting" (2000UW01272, 2004UW06135). These reports were reviewed as an aggregate and no significant new significant safety information about the use of SEROQUEL in children was identified.

5.5.4 Adolescents (age 12 to 18 years; 77 reports)

5.5.4.1 CDS listed topics (20 reports)

Multiple reports for CDS listed topic are contained in Table 44 below.

Table 44 Multiple reports for CDS listed topic (18 reports)

Topic	Report	Primary PT	Serious	Secondary PT	Serious
SOC: General disorders					
Weight increased[a] (4)	2003UW07494	Weight ↑	No	None	NA
	2003UW06764	Weight ↑	No	None	NA
	2003UW01797	Weight ↑	No	Abdominal pain	No
	2003UW01166[b]	Weight ↑	No	Abnormal behavior	No
SOC: Injury and poisoning					
Overdose[c] (4)	2002UW02389[b]	Overdose	No	Abnormal behavior	No
	2002UW02387[b]	Overdose	No	Abnormal behavior	No
	2002UW02386[b]	Overdose	No	Abnormal behavior	No
	2001UW04156[b]	Overdose	Yes	Somnolence Aphasia Agitation Depression Mania	No No No No No
SOC: Nervous system disorders					
EPS[e] (4)	2003UW15096[d]	Tardive dyskinesia	Yes	Dyskinesia Chest pain Vision blurred	Yes No No
	2003UW14877	Dyskinesia	No	Restlessness Bruxism Anorexia	No No No

Table 44 Multiple reports for CDS listed topic (18 reports)

Topic	Report	Primary PT	Serious	Secondary PT	Serious
EPS[e] (4)	2004UW14965	Tremor	Yes	Tongue paralysis	Yes
				Dyskinesia	Yes
				Drooling	Yes
				Palpitations	Yes
				Speech disorder	Yes
	2002UW13956[a,b,f]	Tremor	No	Anorexia	No
				Weight decreased	No
				Weight ↑	No
				Abdominal distension	No
				Breast disorder	No
				Nervousness	No
				Anxiety	No
				Agitation	No
				Hypervigilance	No
Somnolence (6)	2004AP02370[b]	Somnolence	No	Abnormal behavior	No
	2003UW11866	Somnolence	No	None	NA
	2003UW09415	Somnolence	No	None	NA
	2003UW05765	Somnolence	No	Back pain	No
	2001UW06678	Somnolence	No	Insomnia	No
	2000UW02860	Somnolence	No	Sluggishness	No
				Bradycardia	No

[a,b,c,d,e,f] *see sections 6.5, 6.13, 6.14, 6.7, 6.8, and 6.11, respectively for further discussion of these reports,*

Summary for weight increased: Three additional medically unconfirmed reports had "Weight increased" listed as a secondary preferred term (2004UW16531, 2004UW01147, 2002UW13956). For the reports of weight increased, see section 6.5 *Topic of interest; Weight gain* for analysis

Summary for overdose: For the reports of overdose see section 6.14 *Topic of interest; Overdose* for analysis

Summary for EPS: Five additional medically unconfirmed reports had "Dyskinesia" listed as a secondary preferred term (2001UW14363, 2001UW09830, 2001UW02955, 1999UW03979, 1999UW00527). No additional medically unconfirmed reports had "Tardive dyskinesia" listed as a secondary preferred term. One additional non-medically confirmed report had "Tremor" listed as a secondary preferred term (2004UW20338). For the reports of EPS see section 6.8 *Topic of interest: EPS* for analysis.

Summary for somnolence: Eight additional medically unconfirmed reports had "Somnolence" listed as a secondary preferred term (2003UW03398, 2002UW02798,

2004UW17766, 2002SE03015, 2002UW16356, 2004UW05067, 2001UW04156, 2004UW20338).

The AEs reviewed above are listed in the SEROQUEL CDS for the adult population. Following a review of these reports, it was determined that there was no difference in frequency, severity, or characteristics of these events when compared to the known profile of SEROQUEL in adults.

Single report for CDS listed topics

Single reports for CDS listed topic are contained in Table 45 below.

Table 45 Single report for CDS listed topic (2 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Musculoskeletal and connective tissue disorder					
Muscle tightness	2002UW10008	Muscle tightness	No	None	NA
SOC: Nervous system disorders					
Neuroleptic malignant syndrome	2004UW06116	Neuroleptic malignant syndrome	Yes	Granulocytopenia Muscle rigidity Blood creatine phosphokinase ↑ Polyuria Conjunctivitis	No No No No No

Summary for single reports for CDS listed topics

For "Muscle tightness" and "Neuroleptic malignant syndrome," the reports involved a single report for each event (or topic). Therefore, no trends could be identified from these reports. The AEs reviewed above are listed in the SEROQUEL CDS for the adult population. Following a review of these reports, it was determined that there was no difference in frequency, severity, or characteristics of these events when compared to the known profile of SEROQUEL in adults.

5.5.4.2 CDS unlisted topics (57 reports)

Multiple reports for CDS unlisted topics (28 reports)

Multiple reports for suicide are contained in Table 46 below.

Table 46 Multiple reports for serious CDS unlisted topics—Suicidea(3 reports)

Topic	Report	Age /sex	Dose/ TTO	Medical history	Con meds	PTs/Comments
SOC: Psychiatric disorders						

Table 46 Multiple reports for serious CDS unlisted topics—Suicidea(3 reports)

Topic	Report	Age /sex	Dose/ TTO	Medical history	Con meds	PTs/Comments
Suicide	2002UW02601[b] Serious					PTs: Suicide ideation, Mania, Aggression, Hostility, Drug ineffective. See section 6.3 *Suicide*
	1998UW47887 Serious					PTs: Suicidal ideation, Depression, Mood swings, Drug ineffective. See section 6.3 *Suicide*
	1999UW03963 Non-serious					PTs: Intentional self-injury, Fall, Injury, Aphonia. See section 6.3 *Suicide*

Summary for suicide: For further discussion of these three reports, see section 6.3 *Topic of interest; Suicide*. Narratives for serious events in this topic can be found in Appendix B.

AstraZeneca believes that these reports of suicide/suicide attempts (including intentional self injury), and suicidal ideation reflect the background incidence of these events in the schizophrenic and manic populations. There appears to be no signal to suggest that pediatric patients using SEROQUEL are at an increased risk for suicide attempt as a consequence of SEROQUEL therapy or that a causal relationship exists between SEROQUEL therapy and suicide attempt.

Multiple reports for cataract are contained in Table 47 below.

Table 47 Multiple reports for serious CDS unlisted topics—Cataracta (2 reports)

Topic	Report	Age /Sex	Dose/ TTO	Medical history	Concomitant medications	Comments
Cataract (2)	2002UW10010 Non-serious	?/?	Dose unk/ 1 wk	Not provided	Not provided	PT: Cataract No further info.
	2002UW07307 Non-serious	17/F	50 mg/ day approx 6 months	Anger disorder, depression, panic attack, anxiety, obsessive compulsive dis	Unspecified antidepressant	PT: Cataract Seroquel D/c'd. No further info.

[a] see section 6.7 for further discussion of these reports, info=information, d/c'd=discontinued.

Summary for cataract: For further discussion of these reports see section 6.9 *Topic of interest; Cataracts*. These reports of cataracts provided insufficient information and do not establish a causal relationship between cataracts and the use of SEROQUEL in children.

Multiple reports of general disorders are contained in Table 48 below.

Table 48 Multiple reports for non-serious CDS unlisted topics—General disorders (14 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: General disorders and administration site conditions					
Headache (2)	2002SE03015	Headache	No	Somnolence	No
	2002UW16356	Headache	No	Somnolence Anorexia Skin discoloration	No No No
Fatigue (3)	2003UW02268[a]	Fatigue	No	Abnormal behavior	No
	2002UW01405	Fatigue	No	Medication error	No
	1998UW46968	Fatigue	No	Skin depigmentation Scleral discoloration Eye disorder Insomnia	No No No No
Drug ineffective (4)	2004UW04691	Drug ineffective	Yes	None	NA
	2001UW13062	Drug ineffective	No	None	NA
	1998UW48295	Drug ineffective	No	Adjustment disorder Amnesia Fatigue	No No No
	2004UW20338[b]	Therapeutic response decreased	No	Somnolence Muscle twitching Tremor	No No No
Abuse/misuse (2)	2000UW02861	Drug abuser	Yes	None	NA
	2002UW15235	Intentional misuse	No	None	NA
Errors (3)	2003UW11194	Antidepressant drug level	No	None	NA
	2004UW05216	Medication error	No	None	NA
	2004UW04412	Medication error	Yes	Hypersomnia Mood swings Disturbance in attention	No No No

[a,b] see sections 6.13 and 6.8, respectively for a further discussion of these reports.

Summary for general disorders

Summary for headache: Of the two reports of "Headache," one report (2002UW16356) was confounded by a concomitant medication (bupropion) for which headache has been reported. The other report (2002SE03015) described a patient who experienced headache and somnolence four days following the start of SEROQUEL treatment, and immediately following an increase in dose from 50 mg/day to 100 mg/day. SEROQUEL continued and the headache resolved in eight days. One additional non-medically confirmed report

(2003UW10305) had "Headache" listed as a secondary preferred term. This report was confounded by concomitant medications (fluoxetine and gabapentin both for which headache has been reported).

Summary for fatigue: Of the three reports of "Fatigue," one report (2003UW02268) was confounded by concomitant medications (citalopram and topiramate, both for which fatigue has been reported). Another report (2002UW01405) described a patient who experienced fatigue upon receiving SEROQUEL (100 mg), rather than nefazodone as a medication error. No other information including outcome were provided. The third report (1998UW46968) described a patient who experienced fatigue and skin/eye discoloration following at least one month of SEROQUEL therapy (250 mg/day). No medical history or concomitant medications were provided. SEROQUEL discontinued and patient recovered. One additional non-medically confirmed report (1998UW48295) had "Fatigue" listed as a secondary preferred term. The patient became more solitary, exhibited a decreased ability to cope, showed signs of impaired short-term memory and seemed more tired after two months of therapy with SEROQUEL. Prior to SEROQUEL, the patient had previously received treatment with sertraline and dextroamphetamine and experienced a similar effect. SEROQUEL was continued. No further information was available.

Summary for drug ineffective: Of the four reports of drug ineffective, one report (2004UW20338; "Therapeutic response decreased") described a patient with paranoia and night terrors, who experienced twitching, shaking, and somnolence since starting SEROQUEL which lessened with a lower dose. However, the patient stated SEROQUEL only 'works to a degree." No further information provided. Another report (1998UW48295; "Drug ineffective") described a patient who did not experience any improvement in negative symptoms of schizophrenia after two months of SEROQUEL treatment (200 mg/day). No further information regarding drug ineffectiveness was provided. The remaining two reports (2004UW04691; "Drug ineffective," 2001UW13062; "Drug ineffective") contained scant clinical detail and did not lend themselves to analysis. Three additional non-medically confirmed reports (1998UW47887, 2002UW12845, 2002UW02601) had "Drug ineffective" listed as a secondary preferred term. One report (2002UW02601) described a patient who experienced a severe manic reaction and suicidal ideation after four months of SEROQUEL therapy. SEROQUEL was discontinued, and the patient recovered. No further information was available. The other two reports (2002UW12845, 1998UW47887) contained scant clinical detail and did not lend themselves to analysis.

Summary for abuse/misuse: Of the two reports of drug abuse/misuse, one report (2000UW02861; "Drug abuser") was confounded by a medical history of drug abuse and documented medication non-compliance. Another report (2002UW15235; "Intentional misuse") described a patient who took SEROQUEL occasionally to get 'high'. No further information was provided.

Summary for medication error: Of the three reports of error, one report (2004UW05216; "Medication error") described a patient who took an extra SEROQUEL tablet (dose unspecified) at night as a sleep aid. Therefore, the patient ran out of medication 17 days prior

to when the prescription could be refilled. No further information was provided. Another report (2004UW04412; "Medication error") described a patient who received nefazodone instead of SEROQUEL due to a pharmacy dispensing error. The patient experienced somnolence, difficulty concentrating, and mood swings. The patient was gradually taken off nefazodone and restarted on SEROQUEL.

Two additional non-medically confirmed reports (2003UW03398, 2002UW01405) had "Medication error" listed as a secondary preferred term. One report (2003UW03398) described a patient who was dispensed SEROQUEL 300 mg instead of clindamycin. The patient experienced blood shot eyes, disorientation, dry mouth, distorted speech and was catatonic. No further information was available. The second report (2002UW01405) described a patient who had been given a sample of SEROQUEL 100 mg instead of nefazodone. It was reported that the patient felt tired. No further information was provided. Currently, nefazodone has been taken off the European and United States markets.

A last report (2003UW11194; "Antidepressant drug level") contained scant clinical detail and did not lend itself to analysis.

These reports were confounded by concomitant medications or medical history, or provided insufficient information for clinical analysis. Thus, they do not establish a causal relationship between headache, fatigue, drug ineffective, drug abuse/misuse, and medication error and the use of SEROQUEL in the pediatric population.

Multiple reports of memory impairment are contained in Table 49 below.

Table 49 Multiple reports for non-serious CDS unlisted topics— Memory impairment (3 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Nervous system disorders					
Memory impairment (3)	2003UW10460	Memory impairment	No	None	NA
	2002UW02798	Memory impairment	Yes	Mental status changes	Yes
				WBC count ↑	No
				Nasopharyngitis	No
				Dehydration	No
				Somnolence	No
				Confusional state	No
	2004UW17766	Amnesia	No	Somnolence	No

WBC=white blood count, ↑=increased.

Summary for memory impairment: Of the three reports of memory impairment, one report (2002UW02798; "Memory impairment") described a patient who experienced memory impairment following what was believed to be a "concentrated dose" of SEROQUEL. The patient had been successfully treated with SEROQUEL for one year prior to this event. No

further information was available. Another report (2004UW17766; "Amnesia") described a patient who experienced memory loss and fatigue within the first few weeks of SEROQUEL treatment (800 mg/day). SEROQUEL dose was reduced to 700 mg/day. No further information was provided. The last report (2003UW10460; "Memory impairment") contained scant clinical detail and did not lend itself to analysis.

One additional non-medically confirmed report (1998UW48295) had "Amnesia" listed as a secondary preferred term. This report described a patient who became more solitary, exhibited a decreased ability to cope, showed signs of impaired short-term memory and seemed more tired after two months of therapy with SEROQUEL. Prior to SEROQUEL, the patient had previously received treatment with sertraline and dextroamphetamine and experienced a similar effect. SEROQUEL was continued. No further information was available.

These reports provided insufficient information for analysis. Thus, they do not establish a causal relationship between memory impairment and the use of SEROQUEL in children.

Multiple reports for epistaxis are contained in Table 50 below.

Table 50 Multiple reports for non-serious CDS unlisted topics-Epistaxis (2 reports)

Topic	Report	Primary PT	Serious	Secondary PT	Serious
SOC: Blood and lymphatic system disorders					
Epistaxis (2)	2004UW03410	Epistaxis	No	None	NA
	2002UW14380	Epistaxis	No	Visual acuity reduced	No

Summary for epistaxis: Of the two reports of "Epistaxis," one report (2002UW14380) described a patient who experienced epistaxis and poor vision within two months of starting SEROQUEL. Concomitant medication included methylphenidate. Medical history included allergy to sulfa drugs. Further information was not available for additional analysis. Another report (2004UW03410) described a patient who experienced epistaxis within two months of starting SEROQUEL. Concomitant medication included fluoxetine and topiramate. This report contained scant clinical detail and did not lend itself to analysis.

These reports provided insufficient information for clinical analysis. Thus, they do not establish a causal relationship between epistaxis and SEROQUEL and disclosed no significant new safety information about the use of SEROQUEL in children.

Multiple reports for rash are contained in Table 51 below.

Table 51 Multiple reports for non-serious topics—Rash (2 reports)

Topic	Report	Primary PT	Serious	Secondary PT	Serious
SOC: Skin and subcutaneous tissue disorders					
Rash (2)	2003UW15277	Rash	No	None	NA
	2002UW03483	Rash	No	None	NA

Summary for rash: The two reports of "Rash" (2003UW15277 and 2002UW03483) contained insufficient information for clinical analysis. Thus, they do not establish a causal relationship between rash and the use of SEROQUEL in children.

Multiple reports for Enuresis are contained in Table 52 below.

Table 52 Multiple reports for non-serious topics-Enuresis (2 reports)

Topic	Report #	Primary PT	Serious	Secondary PT	Serious
SOC: Renal and urinary disorders					
Enuresis (2)	2000UW03254	Enuresis	No	Thinking abnormal Irritability	No No
	2003SE03466	Enuresis	No	None	NA

Summary for enuresis: One of the two reports of enuresis (2003SE03466) was confounded by the patient's concurrent use of diuretics (unspecified). The other report (2000UW03254) contained scant clinical detail and did not lend itself to analysis.

Single report for CDS unlisted topics (29 reports)

Single reports for CDS unlisted topics are contained in Table 53 below.

Table 53 Single report for topic (29 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
SOC: Cardiac disorders					
QT	2003UW11369[a]	ECG QT prolonged	No	Chest pain	No
SOC: Eye disorders					
Blindness	2001UW01129	Blindness	No	Visual disturbance Syncope	No No
Lens disorder	2001UW06063	Lens disorder	No	None	NA
SOC: General disorders					

Table 53 Single report for topic (29 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Pyrexia	2002UW04019	Pyrexia	No	Back pain Arthralgia Dizziness	No No No
Accident	2002UW09099	Road traffic accident	No	None	NA
SOC: Infections and infestations					
Tonsillitis	2004UW07075	Tonsillitis	No	Vocal cord inflammation Pharyngolaryngeal pain	No No
SOC: Metabolism and nutritional disorders					
Glucose dysregulation	2004UW01147[b,c]	Diabetic ketoacidosis[a]	Yes	DM insulin-dependent[a] Weight ↑[b]	No No
SOC: Musculoskeletal disorder					
Pain	2003UW17098	Pain in jaw	No	Bone pain Neck pain	No No
SOC: Nervous system disorders					
Paraesthesia	2002UW16363	Paraesthesia	No	None	NA
Rigors	2001UW02084	Rigors	No	None	NA
SOC: Psychiatric disorders					
Aggression	2004UW17467[d]	Aggression	Yes	None	NA
Anger	2000UW04354	Anger	No	None	NA
Apathy	1998UW49066	Apathy	No	Disturbance in attention	No
Hallucination, auditory	2004UW05067	Hallucination, auditory	No	Somnolence Anxiety	No No
Eating	1999UW04371	Eating disorder	No	None	NA
Catatonia	2003UW03398	Catatonia	No	Eye redness Disorientation Dry mouth Dysarthria Dizziness Somnolence Medication error	No No No No No No No
Nightmare	2002SE05337	Nightmare	No	None	NA
Delusion	2002UW12845	Delusion	No	Drug ineffective	No
Attention	2002UW03898	Disturbance in attention	No	Dizziness	No

Table 53 Single report for topic (29 reports)

Topic	Report	Primary PT	Serious	Secondary PTs	Serious
Insomnia	2003UW10305[d]	Insomnia	Yes	Vomiting projectile Rigors Haemoptysis Dizziness Headache Screaming Crying Gait abnormal Abnormal behavior	Yes Yes Yes Yes Yes Yes Yes Yes Yes
Obsessive-compulsive	2003UW01372	Obsessive-compulsive disorder	No	None	NA
SOC: Renal and urinary disorders					
Proteinuria	2004UW07472	Proteinuria	No	Pollakiuria	No
SOC : Reproductive system and breast disorders					
Amenorrhea	2004SE03105[e]	Amenorrhea	No	Breast discharge	No
Breast discharge	1999UW03534	Breast discharge	No	None	NA
Pregnancy	2001UW14510	Drug exposure during pregnancy	No	None	NA
Menstruation irregular	2004UW16531[c]	Menstruation irregular	No	Weight ↑ Menorrhagia Emotional disorder	No No No
SOC: Respiratory, thoracic, and mediastinal					
Throat tightness	2004UW14127	Throat tightness	No	Dysphagia Dyspnoea	No No
SOC: Vascular disorders					
Feeling hot	2003UW01902	Feeling hot	No	None	NA
Hot flush	1998AP46892	Hot flush	No	Hyperhidrosis	Unk

[a,b,c,d,e] see sections 6.6, 6.2, 6.5, 6.13, and 6.11, respectively for further discussion of these reports, ECG=electrocardiogram, ↑=increased.

Summary for single report for CDS unlisted topics

In addition to the report contained in Table 53 above, one additional medically unconfirmed report (2003UW10305) had "Chills" listed as a secondary preferred term. In addition to the report contained in Table 52 above, one additional medically unconfirmed report (2002UW02601) had "Aggression" listed as a secondary preferred term. In addition to the report contained in Table 52 above, one additional medically unconfirmed report (2004SE03105) had "Breast discharge" listed as a secondary preferred term. All of these

reports were reviewed as an aggregate for each topic and no new significant safety information was identified.

In addition to the report contained in Table 53 above, two additional medically unconfirmed reports had "Insomnia" listed as a secondary preferred term. One of these reports (2001UW06678) contained scant clinical detail and did not lend itself to analysis. The other report (1998UW46968) described a patient who experienced fatigue and skin/eye discoloration following at least one month of SEROQUEL. SEROQUEL was discontinued. These reports were reviewed as an aggregate and no new significant safety information was identified.

In addition to the report contained in Table 53 above, two additional medically unconfirmed reports had "Disturbance in attention" listed as a secondary preferred term. One of these reports (1998UW49066) described a patient who experienced apathy and a disturbance in attention following three weeks of SEROQUEL treatment. SEROQUEL dose was decreased (100 to 75 mg/day), however, no further information was provided. The other report (2004UW04412) described a patient who received nefazodone instead of SEROQUEL due to a pharmacy dispensing error. The patient experienced somnolence, difficulty concentrating, and mood swings. The patient was gradually taken off nefazodone and restarted SEROQUEL. These reports were reviewed as an aggregate and no new significant safety information was identified.

For the remaining events ("Electrocardiogram QT prolonged," "Blindness," "Lens disorder," "Pyrexia," "Road traffic accident," "Tonsillitis," "Diabetic ketoacidosis" "Pain in jaw," "Paraesthesia," "Anger," "Apathy," "Hallucination, auditory," "Eating disorder," "Catatonia," "Nightmare," "Delusion," "Obsessive-compulsive disorder," "Proteinuria" "Amenorrhea," "Drug exposure during pregnancy," "Menstruation irregular," "Throat tightness," "Feeling hot," "Hot flush"), the reports involved a single report for each event (or topic). Therefore, no trends could be identified from these reports. The reports of "Electrocardiogram QT prolonged," "Diabetic ketoacidosis" "Amenorrhea," "Menstruation irregular," and "Anger" are cross-referenced to section 6.6 *Topics of interest; Prolonged QT*, section 6.2 *Topics of interest; Glucose dysregulation*, section 6.11 *Topics of interest; Hyperprolactinemia and related adverse events*, section 6.5 *Topic of interest; Weight Gain*, and section 6.13 *Topics of interest; Behavioral disturbances*, respectively.

Following a review of this data, no significant new safety issues regarding the use of SEROQUEL in the pediatric population was identified.

6. TOPICS OF INTEREST

6.1 Reports with an outcome of death (11 reports)

Medically confirmed reports

There was one report with an outcome of death in the age group 0 days to 27 days and none in the age group 28 days to 23 months. See Appendix B for the report narrative. This one report

(2003SE05566) described a baby who was born at 37 weeks gestation. The mother took SEROQUEL (600 mg/day) for the last 10 weeks of pregnancy. The baby was delivered without problems, however on Day 2 of life the baby developed intestinal distention, necrotizing enterocolitis (NEC), and compartment syndrome. The baby died one week later and cause of death was reported to be cardiac arrest. No other information was provided. The reporter assessed a causal relationship to the events "due to anticholinergic effects of SEROQUEL." However, section 5.1 *Pharmacodynamic Properties* of the SEROQUEL CDS states:

> "Quetiapine also has high affinity at histaminergic and adrenergic alpha1 receptors, with a lower affinity at adrenergic alpha$_2$ receptors, but no appreciable affinity at cholinergic, muscarinic or benzodiazepine receptors."

Additionally, the incidence of NEC is 1 to 3 cases per 1000 live births (the incidence rate is 1% to 5% of all infants in neonatal intensive care units). Approximately 10% to 35% of infants with NEC are born at term. The clinical course of NEC can vary from a slow indolent process to a fulminant one with progression to death in a few hours (Long 2003). Thus, this report may represent background occurrence. The delivery was without problems and the events began on the second day post-partum.

In the age group two to 11 years, two reports were received that had an outcome of death. See Appendix B for report narratives. In one report of speech disorder (2001UW12073), the temporal sequence of events was not clear. It was unknown if the patient's events occurred directly after a single dose of SEROQUEL was taken or at an unknown amount of time later. Additionally, no information about the patient's medical history was provided, however the patient was on several concomitant medications that would indicate a significant medical history. The second report (2004AC00397) described a child who was physically forced to take SEROQUEL (in a paste like form) and was suffocated. Toxicology exam revealed the SEROQUEL level to be markedly elevated.

In the 12 to 18 years age group, eight reports with a fatal outcome were received. Two reports of "Completed suicide" (2001AP05211, 2001UW06751) are discussed in Section 6.3 *Topic of Interest; Suicide* below. One fatal report of "Overdose" (2003UW10892) is discussed in Section 6.14 *Topic of Interest; Overdose* below.

One report of "Drug toxicity" (2004UW15638) described a patient who died while in the custody of police. This patient had never been prescribed SEROQUEL, however the toxicology report revealed blood levels of SEROQUEL (0.39 mg/L), alprazolam (0.10 mg/L), and hydrocodone (0.07 mg/L). Autopsy also revealed cerebral and pulmonary edema and splenic and pulmonary vascular congestion. The cause of death was reported to be polypharmacy. Another report (2001AP01126) of "Medication error" and "Therapeutic agent toxicity" described a patient who died from heroin poisoning; per the post mortem report.

One report (2000UW03962) of "Arrhythmia," "Pulmonary oedema," "Pulmonary congestion," and "Agitation" described a patient who died from a cardiac arrhythmia after four days of therapy with SEROQUEL. The patient had a history of catecholamine-induced

arrhythmia, exercise induced "double" arrhythmia at an early age, and a markedly abnormal stress test two years earlier, which showed emergence of atrial and ventricular tachycardia accompanied by pre syncope 7-8 minutes into the test. The patient had stopped taking the prescribed propranolol, which was used to treat the arrhythmia, two days prior to her death. The patient's propranolol blood level at the time of death was reported as "low end of therapeutic range." In addition, the patient had received a single dose of haloperidol (for which sudden death has been reported) the day before she was found dead.

Two reports described patients who experienced glucose dysregulation. One report (2002UW05916; "Diabetic hyperosmolar coma") described new onset DM, which can present itself as diabetic coma or non-ketotic hyperosmolar coma. The patient presented with a clinical picture consistent with infection precipitating the hyperosmolar coma. In addition, the report was confounded with a concomitant medication (albuterol) for which DKA and hyperglycemia have been reported and by the patient's obesity. The other report (2003GB01346; "Diabetic ketoacidosis") described a patient who received olanzapine for four months, which was switched to SEROQUEL. The patient died suddenly from DKA approximately five months after starting SEROQUEL. This patient also had a history of obesity. No other information was provided. For more details of these reports see section 6.2 *Topics of interest; Glucose dysregulation* below.

Following a careful review of the reports with an outcome of death, it was determined that the data does not suggest a causal relationship to SEROQUEL. No trends could be identified from these reports. No action is warranted at this time regarding SEROQUEL and death in pediatric patients. AstraZeneca will continue to review all reports with a fatal outcome as part of its ongoing safety surveillance for SEROQUEL.

Medically unconfirmed reports

There were no non-medically confirmed reports with an outcome of death.

Clinical trial reports

There were no reports with an outcome of death received during clinical trials with SEROQUEL.

6.2 Glucose dysregulation (27 reports)

Medically confirmed reports

There were no reports of glucose dysregulation in the age group 0 days to 27 days and none in the age group 28 days to 23 months. In the age groups two to 11 years and 12 to 18 years, there were seven (Table 54) and 18 reports (Table 55) of glucose dysregulation received, respectively. See Appendix B for narratives of these reports.

Table 54 Reports of glucose dysregulation (ages 2 to 11; medically confirmed) (7 reports)

Report #/ Seriousness	Age /Sex	Dose/ TTO	Medical history	Concomitant medications	PTs/Comments
2003UW03648 Non-serious	11/F	Dose/TTO unk	Not provided	Not provided	PTs: Diabetes mellitus Pt developed DM. Outcome + if Seroquel contd unk. No other info.
2004AP00095 Serious	10/F	100 mg/day/ <one mo	Asperger's syndrome	Not provided	PTs: Diabetes mellitus Pt hospitalized with DM w/ ↑BS + ketonuria. Seroquel D/c'd about 3 mos later. DM reported to have resolved that same day. No other info.
2004AP03990 Serious	10/F	100 mg/day/ 108 days	Not provided	Not provided	PTs: Diabetes mellitus insulin-dependent Day 108: ketones in urine, random BS=23. Dx=Type I diabetes. Seroquel D/c'd. Tx=insulin. Pt not yet rec'd. No other info.
2001UW00363 Serious	5/M	50 mg/day / 185 days	Family hx DM, ADHD, speech disorder, enuresis, aggression	Methylphenidate	PTs: Diabetes mellitus insulin-dependent Pt had wt loss, polyuria, + polydipsia. Day 185: BS=500; hospitalized. Dx=juvenile onset DM. Tx=insulin. Seroquel contd. BS monitored 5 to 6x/day. No other info.
2004UW17777 Non-serious	8/F	Dose/TTO unk	Brittle diabetic	Not provided	PTs: Blood glucose increased After starting Seroquel BS went up. No lab data. Outcome + whether Seroquel contd unk. No other info.
2004UW06024 Non-serious	11/ M	Dose unk; ≈6 mos	Not provided	Not provided	PTs: Blood glucose increased Pt had ↑ BS. Tx=oral anti-diabetic med (unspecified). Seroquel D/c'd. BS normalized. Unk if oral anti-diabetic med contd. No other info.
2004UW08948	7/M	300 mg/day; ≈5 mos	Chronic ear infections, sinusitis, asthma, allergy to amoxicillin, lactose intolerance, PDD	Lithium[a,b], carbamazepine, olanzapine[b]	PTs: Hypoglycaemia, Hyperglycaemia, Lipids increased Pt had ↓ BS + ↑ BS. BS fluctuating from 42 (fasting) to 202 (1 hr after fruit), HbA1c =4.9%, GTT =99 (2 hrs post glucose). Pt also had ↑ lipids (no lab data). Seroquel D/c'd w/in one week + BS back to normal. Pt considered rec'd 8 days after event but BS noted to be 186 on that day. No baseline labs. No other info.

[a] for which hypoglycemia has been reported, [b] for which hyperglycemia has been reported, unk or ?=unknown, contd.=continued, info=information, mo(s)=month(s), w/=with, BS=blood sugar, d/c'd=discontinued, dx=diagnosis, tx=treatment, rec'd=recovered, hx=history, ADHD=attention deficit hyperactivity disorder, wt=weight, PDD=pervasive development disorder, HbA1c=glycosylated hemoglobin, GTT=glucose tolerance test, hr(s)=hour(s), w/in=within.

Table 55 Reports of glucose dysregulation (ages 12 to 18; medically confirmed) (18 reports)

Topic Glucose dysregulation (15)	Report	Age /sex	Dose/ TTO	Medical History	Concomitant Medicine	PTs/Comment
	2002UW05916[a] Serious	12/F	600 mg/ day; >10 mos	Mild mental retardation, convulsion, small caliber right coronary ostium, obesity (BMI = 30.4), documented medical non-compliance	Citalopram, desmopressin, oxybutynin, albuterol	PTs: Diabetic hyperosmolar coma, DM non-insulin dependent, Renal failure acute, Leukoencephalopathy, Cardiomegaly, Brain edema, Hyperthermia, Infection, Mental status changes, Blood pressure ↑, Pharyngolaryngeal pain, Abdominal pain, Leukocytosis. Pt in residential facility for 9 mos. Discharge to unspecified place. 6 days later, Pt hospitalized w/ abnormal labs (WBC=18.3K, creatinine =3.2 mg/dL, HbA1c=11.3%) + AEs listed below. Tx=potassium, cefotaxime, midazolam , acetaminophen. Pt became unconscious 12 hrs later and died. Autopsy findings consistent w/ leukoencephalopathy etiology unk.
	2003GB01346[a] Serious	18/F	200 mg/ day; 8 mos	Obesity, wt ↑ on olanzapine[b]	Not provided	PTs: DKA, Tinea cruris Pt D/c'd olanzapine d/t ↑wt + Seroquel started. W/in 2 mos Pt had fungal groin infection "which was noted to be associated w/ DM." 2 mos later, Pt hospitalized w/ abdominal pain, vomiting, collapse. Dx=DKA. Tx initiated (unspecified). Pt died 3 days later.

Table 55 Reports of glucose dysregulation (ages 12 to 18; medically confirmed) (18 reports)

Topic Glucose dysregulation (15)	Report	Age /sex	Dose/ TTO	Medical History	Concomitant Medicine	PTs/Comment
	2001UW00231[e] Serious	12/F	150-600 mg/ day; 6 wks	BG ↑ while on olanzapine, questionable family hx of DM	Venlafaxine, irbesartan, mirtazapine, multivitamins, medroxy-progesterone, lorazepam	PTs: DM, Wt increased Wt ↑ 32 lbs, BG ↑. Tx=insulin. Pt discharged home. No further info.
	2002AP04001 Serious	16/F	Dose unk; 12 wks	Bipolar disorder, convulsion, family hx DM	Valproate[c]	PTs: DM. Urine positive for ketones, glucose, + protein. Wt + BMI ↑. Tx=change in diet. BG controlled. No other info.
	2000UW00266 Serious	12/ M	300 mg/ day; >4 mos	Not provided	Sertraline, clonazepam, haloperidol[s], valproate[c]	PTs: DM. Pt hospitalized w/ BG of 863 mg/dL. Seroquel d/c'd. Tx=insulin. BG ↓ to 170 mg/dL. Pt recovering. No other info.
	1999UW00967 Non-serious	17/ M	400 mg/ day; TTO unk	Not provided	Paroxetine, valproate[c]	PTs: DM Routine lab work revealed DM. Tx=glipizide. Seroquel contd. No other info.
	2002AP01607 Serious	17/F	600 mg/ day; >3 mos	Bipolar disorder, conduct disorder, mild mental retardation	Valproate[c], paroxetine	PTs: DM non-insulin dependent, BG abnormal, Hyperlipidemia Pt had BG of 300mg/dL + hypertriglyceridemia. Wt + BMI ↑. Tx=metformin, risperidone, + valproate. FBS ranged from 99-170 mg/dL. Seroquel d/c'd. No other info.
	2002UW12946 Non-serious	14/F	50 mg/day; TTO unk	Uncontrolled diabetic, non-compliance w/ insulin	Insulin	PTs: DM inadequate control Pt uncontrolled diabetic prior to Seroquel. Now on low dose Seroquel + still uncontrolled. Pt previously non-compliant w/ insulin. Pt outcome unk. No other info.

Table 55 Reports of glucose dysregulation (ages 12 to 18; medically confirmed) (18 reports)

Topic Glucose dysregulation (15)	Report	Age /sex	Dose/ TTO	Medical History	Concomitant Medicine	PTs/Comment
	2004GB00610 Serious	17/ M	25 to 100 mg/ day; 10 days	Sedation, smoker	Valproate[c], lorazepam, procyclidine, haloperidol, risperidone[d], clonazepam	PTs: DKA On Day 10 Pt had ↑BP, confusion, drowsiness, polyuria, polydipsia, ketonuria, ↑ thirst. BG > 50 mmol/L. Dx=severe DKA. Tx= IVF, insulin. Seroquel d/c'd. Risperidone also d/c'd on unk date after starting Seroquel. Pt rec'd.
	2000UW02905 Serious	18/?	Dose/TT O unk	Not provided	Sertraline	PTs: DKA[a], Pancreatitis acute, Lipids ↑ Pt hospitalized w/ BG of 1200 mg/dL, acute pancreatitis, + ↑lipids. Tx + Pt outcome unk. No other info.
	2004UW18892 Non-serious	12/ M	400 mg/ day; TTO unk	Metabolic syndrome, acanthosis nigricans	Lithium[c], imipramine	PTs: Blood insulin increased. Pt had ↑insulin levels. Unk if Seroquel contd. Pt not yet rec'd. No other info.
	2004UW15170 Non-serious	12 to 14/F	Dose/TT O unk	Fetal alcohol syndrome	Clonidine, guanfacine, dextro-amphetamine/ amphetamine, immunoglobulins	PTs: BG increased. Pt developed post prandial BG "in the 200s." FBS=normal, HbA1c=5%. Pt outcome + if Seroquel contd was unk. No other info.
	2004UW04671 Serious	17/ M	Dose/TT O unk	Not provided	Not provided	PTs: BG increased BG=1000. Tx=glucose tolerance test. Pt outcome + if Seroquel contd. was unk. No other info.
	2002UW14424 Non-serious	18/ M	150 mg/ day; TTO unk	DM insulin-dependent	Methylphenidate	PT: BG increased BG ↑ to 400-500 mg/dL after does of Seroquel ↑. Pt outcome + if Seroquel contd. is unk. No further info.

Table 55 Reports of glucose dysregulation (ages 12 to 18; medically confirmed) (18 reports)

Topic Glucose dysregulation (15)	Report	Age /sex	Dose/ TTO	Medical History	Concomitant Medicine	PTs/Comment
	2002UW14927[c] Non-serious	13/F	50-600 mg/ day; 2 mos	No prior hx of insulin resistance or ↑BG	Valproate[c]	PTs: Hyperglycemia, Wt ↑ After 2 mos on Seroquel FBS=138 mg/dL + urine glucose > 1000 mg/dL. Pt outcome + if Seroquel contd. is unk. No further info.
	2001UW14447 Serious	13/ M	300 mg/ day; <2 mos	Morbid obesity	Valproate[c]	PTs: Arrhythmia, Myocardial ischemia, DKA. Pt developed cardiac situation (arrhythmia progressing to ischemia). Stress test + for ischemia. Pt subsequently developed DKA + treated w/ insulin. Pt was in foster care, may be family hx of DM in grandparents + mother. Seroquel contd. Pt outcome unk. No other info.
	2004UW15424 Serious	12/ M	700 mg/ day; 11 mos	Family hx DM	Buspirone, tomoxetine	PTs: Abnormal behaviour, BG increased After 11 mos on Seroquel BG ↑ from 105 (unk if prior to Seroquel) to 170-225. Tx=monitor BG 3x/day. Seroquel d/c'd. BG normalized w/in 2 wks (no BG value). Unk if BG values were random or fasting. No other info.
	1999UW03387 Non-serious	17/ M	50 mg/day; 6 mos	Tx w/ risperidone[d] prior to Seroquel	Methylphenidate, nefazodone	PTs: Somnolence, DM non-insulin dependent. After 6 mos on Seroquel Pt diagnosed w/ Type II DM. 2 mos later Seroquel dose ↓ to 25 mg/day. Pt had received risperidone prior to Seroquel. Seroquel contd. Pt outcome unk.

[a,e,f] these reports are also discussed in sections 6.1, 6.5, and, 6.13, respectively, [b] for which DM and fatal DKA have been reported, [c] for which hyperglycemia has been reported, [d] for which DM has been reported, mo(s)=month(s), BMI=body mass index, w/=with, WBC=white blood cell, HbA1c=glycosylated hemoglobin, tx=treatment, hr(s)=hour(s), unk or ?=unknown, wt=weight, d/c'd=discontinued, d/t=due to, w/in=within, dx=diagnosis, DKA=diabetic ketoacidosis, wk(s)=week(s), BG=blood glucose, info=information, hx=history, contd.=continued, FBS=fasting blood sugar, BP=blood pressure, IVF=intravenous fluids, rec'd=recovered

In the age group two to 11 years, of the seven medically confirmed reports involving patients who experienced glucose dysregulation, two reports (2001UW00363, 2004AP03990) described patients who were diagnosed with Type I DM. Type I DM is unlikely to be caused by drugs (Naik et al. 2003). One of these two reports (2001UW00363) involved a patient who had a family history of DM. Another of the seven reports (2004UW08948) described a patient who experienced both hypoglycemia and hyperglycemia. This report was confounded by concomitant medications for which hyperglycemia (olanzapine, lithium) and hypoglycemia (lithium) have been reported. Another report (2004AP00095) contained incomplete information. It was reported that the patient started SEROQUEL the same month that she developed DM, however, it was unclear whether the patient had taken SEROQUEL prior to the event. Additionally, no laboratory data was provided. The remaining three reports contained scant clinical detail and did not lend themselves to analysis (2004UW17777, 2003UW03648, 2004UW06024). In one of these three reports (2003UW03648) the reporter thought that the "child might have been predisposed" to DM.

In the age group 12 to 18 years, of the 18 medically confirmed reports of glucose dysregulation, two reports (2002UW05916: "Diabetic hyperosmolar coma," 2003GB01346: "Diabetic ketoacidosis" [DKA]) had a fatal outcome and are discussed in section 6.1 *Topic of Interest; Reports with an outcome of death* above. One of the fatal reports (2002UW05916) described a patient with mental retardation and a seizure disorder, who had received SEROQUEL for more than nine months. She was exceptionally tall and obese and had not complied for scheduled examinations to determine the cause of this condition. The SEROQUEL dose was increased (400 to 600 mg/day) about one month before the event. The patient experienced diabetic hyperosmolar coma, DM non-insulin-dependent, acute renal failure, leukoencephalopathy, cardiomegaly, brain edema, hyperthermia, infection, mental status changes, increased blood pressure, sore throat, abdominal pain, and leukocytosis. Laboratory data included blood glucose (1779 mg/dL), white blood cell count (18.3 K), creatinine (3.2 mg/dL), blood urea nitrogen (54 mg/dL), and hemoglobin (11.3%). Treatment included potassium, cefotaxime, versed for agitation, and acetaminophen. Less than 12 hours later, the patient became unconscious and died with a temperature of 111°F. It was reported that the patient had an unspecified infectious process that may have precipitated the coma. However, the autopsy indicated no infection, enlarged liver, mild brain edema, perivascular atrophy of the white matter, interstitial fibrosis in the heart, pancreatic degranulation of the acinar cells, and lipid depletion from adrenal cortical cells. The report was confounded by concomitant medications including citalopram, for which gastrointestinal disturbances such as nausea, vomiting, dyspepsia, constipation, and diarrhea have been reported; desmopressin, for which mild abdominal cramps have been reported; oxybutynin, for which nausea and vomiting have been reported; and salbuterol, for which muscle cramps, nausea, vomiting, and hyperglycemia have been reported. The other report (2003GB01346) described a patient with a medical history of obesity, who discontinued olanzapine after 3 1/2 months due to weight gain, and immediately commenced therapy with SEROQUEL. Within two months the patient developed a fungal groin infection "which was noted to be associated with DM." Two months later the patient had abdominal pain, vomiting, and collapsed. The patient was reported to have experienced DKA, received unspecified treatment, and died three days later. No other information was provided.

Three other reports of DKA described patients with no reported prior history of DM. One of the three reports (2001UW14447) was confounded by the patient's morbid obesity (BMI=38.7 kg/m^2). Another of the three reports (2004GB00610) was confounded by a concomitant medication (risperidone) for which DM has been reported and the third report of DKA (2000UW02905) contained scant clinical detail and did not lend itself to analysis.

Six reports described patients who developed new-onset DM. Three of the six reports were confounded by a concomitant medication (2002AP01607: valproate, 1999UW00967: valproate, 1999UW03387: risperidone) for which hyperglycemia or DM has been reported. Another of the six reports (2000UW00266) described a patient who was diagnosed with Type I DM, which is unlikely to be drug related. This patient was also taking a concomitant medication (valproate) for which hyperglycemia has been reported. Another of the six reports (2002AP04001) was confounded by the patient's family history of DM and a medication (valproate) for which hyperglycemia has been reported. The sixth report (2001UW00231) was confounded by the patient's possible family history of DM and history of increased blood glucose while on olanzapine (for which DM has been reported).

Another report (2002UW12946) described a patient with a history of uncontrolled DM and insulin non-compliance who experienced uncontrolled DM. Four other reports described patients who had no history of DM and experienced hyperglycemia. One of the four reports (2002UW14927) was confounded by a concomitant medication (valproate) for which hyperglycemia has been reported, another (2004UW15424) was confounded by the patient's family history of DM, and the other two reports (2004UW04671, 2004UW15170) contained scant clinical detail and did not lend themselves to analysis. Another report (2002UW14424) described a patient with a history of juvenile DM who experienced increased blood sugars. This report (received from a sales representative) contained scant clinical detail and did not lend itself to analysis. The physician instructed the company not to contact him for further information. The last report (2004UW18892) described a patient who experienced increased blood insulin and was confounded by the patient's history of metabolic syndrome.

Non-medically confirmed reports

There were no reports of glucose dysregulation in the age group 0 days to 27 days or in the age group 28 days to 23 months. In both the age groups two to 11 years and 12 to 18 years respectively, there was one report of glucose dysregulation each. These are summarized in Table 56 below. Both reports (2004UW19755, 2004UW01147) contained scant clinical detail and did not lend themselves to analysis.

Table 56 Reports of glucose dysregulation (ages 2 to 11 and 12 to 18; non-medically confirmed) (2 reports)

Report #/ Seriousness	Age /Sex	Dose/ TTO	Medical history	Concomitant medications	PTs/Comments
2004UW19755 Non-serious	11/ M	Dose unk/ <one mo	Not provided	Dextroamphetamine, aripiprazole	PTs: DM, Constipation, Abdominal pain upper. Pt developed DM, constipation, stomach pain. Outcome + if Seroquel contd is unk. No other info.
2004UW01147[a]	14/F	25 mg/d ay; 5 years	Not provided	Not provided	PTs: DKA, DM insulin-dependent, Wt increased. Pt BMI=23.1 (date unk). After about 5 years on Seroquel, Pt developed brittle DM. Pt also had DKA + wt gain. Tx=insulin. Pt outcome unk. Seroquel contd. + then d/c'd >5 mos later (reason unspecified). No further info.

[a] this report is also discussed in section 6.5, unk=unknown, mo(s)=month(s), contd=continued, info=information, BMI=body mass index, DKA=diabetic ketoacidosis.

Clinical trial reports

There were no reports in the pediatric population of glucose dysregulation received during clinical trials with SEROQUEL.

Literature

One prospective study was a 12-week, open-label study in antipsychotic naïve subjects (age 5-18 years; total n=71 [SEROQUEL n=9]) with psychotic, mood, and/or disruptive behavior-spectrum disorders (Correll et al 2004). The study results were available only as an abstract and provided limited information. Measurements (taken at baseline, four, and 12 weeks) included height, weight, fat mass and percentage, waist circumference, fasting glucose, insulin, prolactin, leptin, and second-generation antipsychotic (SGA) levels. This study stated that fasting glucose, insulin, and insulin resistance increased significantly. In addition, the study concluded that SGAs did not differ in their effect on glucose and insulin, or on absolute and relative HOMA-IR changes (olanzapine: 0.87 ± 1.6=62.7%, SEROQUEL: 0.75 ± 1.2=24.5%, risperidone: 0.62 ± 1.6=49.5%, P=0.84 and P=0.56, respectively). Glucose increase was correlated with stimulant use, and increases in weight, BMI, and fat percentage. Insulin and HOMA-IR changes were correlated with disruptive behavior-spectrum disorders, non-Caucasian, non-Hispanic race, and weight gain. The percent increase in HOMA-IR was correlated with increased waist circumference, Asian race, and stimulant co-treatment. One pre-morbidly obese youngster developed DM. This study appears to be a nonrandomized study with a small number of SEROQUEL subjects. The lack of a control (e.g. placebo) group limits the interpretation of the data. For example, the effects may have been due to entering a treatment program. Since there were no baseline data reported (one subject was

reportedly obese), it is unknown to what extent the subjects had underlying risk factors for insulin resistance. The lack of statistically significant differences between the treatment effects is not surprising, given the relatively small sample size. However, the effect on relative HOMA-IR was numerically smallest for SEROQUEL (24.5%) compared to risperidone (49.5%) and olanzapine (62.7%). The discrepancy between the absolute and relative changes in HOMA-IR suggests that the SEROQUEL patients may have had higher baseline HOMA-IR values. In summary, due to small number of study subjects, limited information, and apparent lack of randomization, no conclusions can be drawn from the study. (This study is also discussed in section 6.5 *Topic of Interest; Weight gain.)*

Summary for glucose dysregulation

Following a review of all the reports, it was determined that assessment of causality was not possible in these cases because of incomplete clinical information, unclear temporal sequence of exposure and outcome, confounding by concomitant medications for which DM or related events have been reported, risk factors for DM (e.g. obesity or family history of DM), and/or alternative explanations. In summary, these data, along with the medical/scientific literature, do not establish a causal relationship between SEROQUEL and new-onset DM or worsening of preexisting DM in children. AstraZeneca will continue to keep reports of DM and related disorders under careful review.

6.3 Suicide (11 reports)

Medically confirmed reports

There were no reports of suicide in the age group 0 days to 27 days or in the age group 28 days to 23 months. In the age groups two to 11 years and 12 to 18 years, there were one and seven reports of suicide, respectively. See Appendix B for narratives of these reports.

In the age group two to 11 years, one report (2004UW14830) described a patient who had been taking SERQOUEL for a year when he suddenly experienced anxiety, suicide attempt, depression, mood swings, anger, and obsessive thoughts after taking SEROQUEL from a new refill. The patient was given a new lot of SEROQUEL and the events resolved (which could indicate some type of medication error). No further information was provided.

In the age group 12 to 18 years, two reports of "Completed suicide" (2001AP05211, 2001UW06751) were received from the literature report *The 2000 Annual Report of the American Association of Poison Control Center (*AAPCC). The AAPCC report details the results of the data compiled by the toxic exposure surveillance system (TESS) from human exposure cases reported in 2000. These reports are presented as a line listing with limited information. Both of these patients committed suicide with multiple medications including SEROQUEL (2001AP05211: valproate, bupropion, 2001UW06751: paroxetine). These two cases contained scant clinical detail and did not lend themselves to analysis.

Another three reports of "Suicide attempt," described patients who attempted suicide by overdose and are also referenced in section 6.14 *Topic of Interest; Overdose*. Two of these three reports were confounded by both the patients' medical histories (2004AP01560:

depression, prior overdose, 2001AP00830: depression) and a concomitant medication, which has been reported to have an increased risk of suicide in children and adolescents (2004AP01560: fluvoxamine, 2001AP00830: sertraline). The third report (2002UW13817) described a patient with end stage liver disease who took an overdose, slit his wrists, and stabbed his stepfather. This report contained limited information for assessment, as no information regarding the patient's concomitant medications or outcome was provided. The last two reports of "Suicidal ideation" (2004UW06809, 2004UW09606) contained scant clinical detail and did not lend themselves to analysis.

Medically unconfirmed reports

There were no reports of suicide/suicide ideation in the age groups 0 days to 27 days, 28 days to 23 months, or two to 11 years. There were three reports of suicide/suicide ideation/intentional self injury in the 12 to 18 years age group. These reports are summarized in Table 57 below.

Table 57 Reports of suicide (ages 12 to 18; non-medically confirmed) (3 reports)

Report	Age /sex	Dose/ TTO	Medical history	Concomitant medications	PTs/Comments
2002UW02601 Serious	13/ M	Dose unk; 4 mos	Not provided	Gabapentin, topiramate, clonazepam	PTs: Suicide ideation, Mania, Aggression, Hostility, Drug ineffective Event occurred after 4 mos of Seroquel + after taking one clonazepam tablet. Had previous hx of same events w/ clonazepam in the past. Pt rec'd.
1998UW47887 serious	17/F	300 mg/ day; 18 days	Not provided	Clozapine, valproate, lorazepam	PTs: Suicidal ideation, Depression, Mood swings, Drug ineffective. Event 18 days after switching from clozapine to Seroquel. No further info.
1999UW03963 non-serious	18/F	Dose unk; 2 days	Not provided	Not provided	PTs: Intentional self-injury, Fall, Injury, Aphonia. Event 48 hours after 1st Seroquel dose. Pt chewed fingers "as if food," fell, lost voice, + was thrown against wall as if by external force. Seroquel D/c'd; events subsided.

unk=unknown, mo(s)=month(s), hx=history, w/=with, rec'd=recovered, info=information, d/c'd=discontinued.

One of the three reports (1998UW47887: "Suicide ideation") described a patient who experienced depression and mood swings after which the dose of SEROQUEL was increased. This report was confounded by concomitant medications (valproate; for which confusion, aggression, hyperactivity, and behavioral disturbances have been reported, and lorazepam; for which confusion, depression, changes in libido, visual disturbances, hostility, aggression, and disinhibition have been reported). In addition, this report contained scant clinical detail and did not lend itself to analysis. Another report (2002UW02601; "Suicide ideation") described a patient who was taking gabapentin, topiramate, and clonazepam as concomitant medications and experienced a severe manic episode (including being suicidal) after taking SEROQUEL.

The patient had experienced similar incidences after taking clonazepam (prior to commencing SEROQUEL) in the past. Both SEROQUEL and clonazepam were discontinued and the patient did not experience any further symptoms. No further information was provided. The last report (1999UW03963; "Intentional self-injury") described a patient who experienced an episode of falling down, chewing her fingers, losing her voice and throwing herself against a wall, after taking SEROQUEL for two days. The patient discontinued SEROQUEL and the symptoms gradually subsided. No medical history, concomitant medications, or further information was provided.

It is estimated that between four and 13% of people with schizophrenia commit suicide and between 25 and 50% make a suicide attempt (Meltzer HY 2001). Mortality with bipolar illness averages 2 to 2.5 times the expected rate for that age; twenty-five to fifty percent of patients with bipolar illness attempt suicide at least once (Jacobson 2001) and completed suicide occurs in an estimated 8% to 15% of individuals with the disease; making it one of the most serious and deadly psychiatric illnesses. (Goldman 2000).

Thoughts of suicide are common in the normal adolescent population. One in four females and one in seven males report seriously considering suicide in a one-year period. About two million adolescents aged 13 to 19 years attempt suicide each year, and 700,000 of them receive medical attention for these attempts. Two thousand adolescents actually commit suicide each year making it the third leading cause of death among those aged 15 to 24 years. Worldwide there are an estimated 300,000 suicide attempts. Thirty thousand adolescents worldwide commit suicide. The cumulative prevalence of suicide attempts in the adolescent population has been estimated at 3% (Kennedy et al 2004, Murphy 1998).

The overwhelming proportion of adolescents who commit suicide (over 90%) suffered from an associated psychiatric disorder at the time of their death. Suicidal thoughts are common in children and adolescents and are not always associated with other features of psychopathology. Disruptive, mood, and anxiety disorders increase the risk of suicidal ideation in children and adolescents, and substance use or separation anxiety may provoke adolescents with ideations to attempt suicide (Shaffer et al 2001).

Following a careful review of all these reports, AstraZeneca has concluded that the reports of completed suicide/suicide attempt and suicidal ideation reflect the background incidence of these events in the schizophrenic and bipolar (mania) population. There appears to be no signal to suggest that patients using SEROQUEL are at an increased risk for suicide attempt as a consequence of SEROQUEL therapy. Therefore, it was determined that the data do not establish a causal relationship between SEROQUEL and suicide/suicide attempts and suicidal ideation in children. AstraZeneca will continue to review reports of suicide/suicidal ideation in children as part of its ongoing safety surveillance for SEROQUEL.

Clinical trial reports

There were three serious reports of suicide or intentional self injury received during clinical trials with SEROQUEL. One report of suicide attempt (2002PK00588) and one report of depression suicidal (2004AP02997) were confounded by the patients' concurrent depression.

One report of intentional self-injury (2004AP02999) was confounded by the patient's concurrent depression and by concomitant medications (venlafaxine, sertraline) for which a possible increased risk of suicidal ideation and suicide attempts has been reported in children and adolescents. All three of these reports were considered not related by the investigators.

6.4 Agranulocytosis (1 report)

There were no reports of agranulocytosis in the age groups 0 days to 27 days, 28 days to 23 months, or two to 11 years. One report of "Agranulocytosis" was received for the age group 12 to 18 years. This report (1999UW01989) described a patient who had a history of severe neutropenia (four months prior to this event) due to an unknown cause; this patient's absolute neutrophil count (ANC) reached a nadir of 74 but the patient was asymptomatic. SEROQUEL was discontinued and the patient recovered. See Appendix B for a narrative for this report. Assessment of causality was difficult for this report due to confounding by a recent medical history of severe neutropenia from an unknown cause.

The Council for International Organizations of Medical Sciences (CIOMS) defines agranulocytosis as severe neutropenia (< 0.5 $x10^9$/L neutrophils) with a sudden onset of the signs and symptoms of bacterial infection such as fever, malaise, prostration, and typical presentation with oropharyngeal or anorectal lesions. The patient was asymptomatic, therefore, this report did not meet the criteria for agranulocytosis according to CIOMS. This report did not establish a causal relationship between SEROQUEL and agranulocytosis in children. (Neutropenia is listed in the SEROQUEL Core Data Sheet). AstraZeneca will continue to review reports of agranulocytosis in children as part of its ongoing safety surveillance for SEROQUEL.

Clinical trial reports

There were no reports in the pediatric population of agranulocytosis received during clinical trials with SEROQUEL.

6.5 Weight gain (51 reports)

Medically confirmed reports

There were no medically confirmed reports of weight gain in the age groups 0 days to 27 days or 28 days to 23 months. There were 12 medically confirmed reports of weight gain in the two to 11 years age group and 31 reports in the 12 to 18 years age group.

In the two to 11 years age group, four of the 12 reports were confounded by concomitant medications for which weight gain has been reported (2004UW12495: valproate, 2004UW07409: oxcarbazepine, 2004UW07567: valproate, 2004UW19620: lithium, risperidone). The remaining eight reports (2001UW02582, 2001UW10154, 2001UW10901, 2002UW03308, 2004UW15668, 2004UW10733, 1999AP05794, 1999AP05734) contained scant clinical detail and did not lend themselves to analysis.

In the 12 to 18 years age group, 10 of the 31 medically confirmed reports were confounded by concomitant medications for which weight gain has been reported (2004AP01466: lithium,

2003AP04059: valproate, 2004UW12118: valproate, risperidone, 2003SE04649: perphenazine, 2002UW14927: valproate, 2002UW10888: valproate, lithium, 2001UW00231: medroxyprogesterone, 2001AP05884: sulpiride, 2004UW11289: valproate, 2001AP05633: risperidone). One of these 10 reports (2004UW11289) described a patient who was hoarding and eating a lot of candy. Another of the 10 patients (2001AP05633) lost the weight that they had gained without dieting while continuing SEROQUEL.

Another report (2003AP03696) described a patient with a history of bulimia who felt better while taking SEROQUEL but began to gain weight and so resumed the bulimic behaviors. SEROQUEL was tapered off over the next two months, however the patient continued to gain weight after SEROQUEL was discontinued. Another report (2004AC00232) described a patient who was experiencing hyperphagia and a decreased level of activity. Another patient (2003UW14488) was reported to "experience rapid severe weight gain," however, the baseline (prior to starting SEROQUEL) weight and the weight at the time of the event (after taking SEROQUEL for 10 months), was a two-pound difference.

The remaining 18 reports contained scant clinical detail and did not lend themselves to analysis (2004UW17672, 2004UW07449, 2004PK00373, 2003UW14739, 2003UW13102, 2003UW07708, 2003UW00732, 2002UW02962, 2002SE01178, 2001UW15552, 2001UW09625, 2000AP05542, 2003UW16130, 2003UW14541, 2002GB01559, 1999AP05792, 1999AP05733, 1999AP04948).

Medically unconfirmed reports

There were no medically unconfirmed reports of weight gain in the age groups 0 days to 27 days or 28 days to 23 months. In the two to 11 years age group and the 12 to 18 years age group, there were one and seven medically unconfirmed reports of weight gain, respectively.

In the two to 11 years age group, the one report (2004UW16895) was confounded by a concomitant medication (valproate) for which weight gain has been reported.

In the 12 to 18 years age group, three of the seven reports were confounded by concomitant medications (2003UW01797: valproate, 2004UW16531: lamotrigine, citalopram, 2002UW13956: medroxyprogesterone, risperidone) for which weight gain has been reported. One of these patients (2002UW13956) was reported to have experienced both an increase and decrease in weight. The other four reports contained scant clinical detail and did not lend themselves to analysis (2003UW07494, 2003UW06764, 2003UW01166, 2004UW01147).

In section 4.8 *Undesirable effects* of the SEROQUEL CDS, weight gain is listed with a frequency of common. In addition, the footnote associated with weight gain in the CDS states:

> "Occurs predominately during the early weeks of treatment."

It is not uncommon for children to fluctuate in weight especially during pre-pubescence and puberty. Assessment of causality was difficult in most of these cases because of either scant clinical detail, unclear temporal sequence between exposure and outcome, or confounding by

concomitant medications or illness. Therefore, although SEROQUEL can cause weight gain in adults, it is unclear from these reports if weight gain is a safety concern in pediatric patients. Taken together, it was determined that the data do not disclose any significant new safety information about the use of SEROQUEL and weight gain in children.

Clinical trial reports

There were six pediatric patients who experienced seven (all non-serious) events of weight gain during clinical trials with SEROQUEL. Four of these events were assessed as causally related and three were assessed as not-causally related by the investigator.

Literature

Five studies (two prospective/three retrospective) looked at changes in weight and/or body mass index (BMI) in children and/or adolescents taking atypical antipsychotics including SEROQUEL. All of these studies showed that, when compared to risperidone and/or olanzapine, SEROQUEL is associated with the least amount of weight gain. In a 12-week, prospective, open-label study in subjects 5 to 18 years old (n=141) with psychotic, mood, and/or aggressive disorders monthly height, weight, BMI, fat mass and percentage, and waist circumferences were measured. At baseline, four, and 12 weeks, leptin and antipsychotic levels were assessed. In the 141 patients who completed 0.8 weeks (mean=12.0 ± 1.5) of treatment there was a significant increase in weight, BMI, fat mass and percentage, and waist circumferences. All measures increased with olanzapine most significantly (n=50; 15.3 ±10.9 lbs=2.4 ± 1.7 BMI points), followed by risperidone (n=52; 10.7 ± 8.2 lbs=1.6 ± 1.3 BMI points) and quetiapine (n=41; 5.0 ± 11.4 lbs=0.6 ± 2.0 BMI points). In antipsychotic naïve patients (n=74), olanzapine caused significantly higher increases only in fat percentage and abdominal circumference compared to quetiapine ($p<05$, respectively). Correlates of weight gain at endpoint were weight gain at four weeks and baseline to endpoint increases in leptin ($p<0001$, respectively), co-treatment with divalproex ($p<01$), antipsychotic-naïveté ($p=0.03$), and diagnosis of schizophrenia-spectrum disorders ($p<05$). The authors concluded that high-risk individuals who experience largest weight gain are antipsychotic-naïve, leptin resistant youngsters with schizophrenia-spectrum disorders, and are co-treated with divalproex (Correll et al 2004). One other prospective study was a randomized open-label, eight-week study of monotherapy with atypical antipsychotics (olanzapine [n=19], quetiapine [n=19], risperidone [n=42], ziprasidone [n=21]) in the treatment of youth (10.2 ± 2.7 years of age) with mania. Seventy-one percent of the patients completed the study with no differences in rate of dropout between the medication arms. Olanzapine was associated with marked increased in weight (4.9 ± 2.1 kg increased) that was statistically significantly greater than the weight gain for risperidone (2.2 ± 2.1 kg), quetiapine (1.4 ± 1.6 kg), and ziprasidone (0.6 ± 2.1 kg) (Mick 2004). Both of these studies were presented in abstract form only.

Two of the three retrospective studies examined children and adolescents taking SEROQUEL, risperidone, or olanzapine. One of these studies (reported as an abstract) reviewed baseline and six consecutive monthly weight and height measurements of 26 children receiving atypical antipsychotics (SEROQUEL n=8, risperidone n=14, olanzapine n=4). Repeated measures analyses of variance controlling for age, sex, initial weight, duration of treatment,

and placement on a weight reduction program revealed statistically significant difference between the groups in the final weight change. Mean weight change was highest in the olanzapine group (+6.53 kg) and lowest in the quetiapine group (-0.21 kg). The authors concluded that atypical antipsychotics cause weight gain in children and adolescents and that the weight gain patterns seem to correlate with differential affinity for histamine H_1 receptors in adult males (Ibikunle 2001). In a study (reported as an abstract) by Grcevich (Grcevich S, 2000) the medical records of 97 patients treated between January 1995 and June 1999 were reviewed. Seventy-five patients were treated with risperidone, 25 patients with quetiapine, and 16 with olanzapine. It was noted by the authors that weight gain was a more common side effect observed with all three agents. After three months of treatment the mean weight gain was 14.1 lbs for olanzapine, 8.6 lbs for risperidone, and 7.3 lbs for quetiapine. The authors concluded that patients receiving quetiapine were less likely to gain weight during the first three months of therapy compared to those on olanzapine. It was also noted during the chart review that extrapyramidal side effects required treatment in seven of 75 patients receiving risperidone, four of 16 patients receiving olanzapine, and none of the quetiapine patients. Another retrospective study (Patel 2004) examined the changes in short-term weight and BMI in children and adolescents receiving olanzapine and SEROQUEL. Patients were excluded if they had taken any antipsychotic agent within six months before the start of therapy. Fifty patients received treatment with olanzapine and 53 patients received therapy with SEROQUEL. At baseline SEROQUEL treated patients had significantly greater weights and BMIs than those receiving olanzapine (22% of olanzapine patients were considered to be overweight; 49% SEROQUEL patients were considered to be overweight). After correcting for baseline values, increases in weight and BMI were significantly greater in the olanzapine than the SEROQUEL group. The average weight gain and BMI increase in the olanzapine group was 3.8 kg and 1.3 kg/m^2, respectively and the average weight gain in the SEROQUEL group was 0.03 kg and the BMI decreased by 0.2 kg/m^2. The authors concluded that the weight gain and increases in BMI were more strongly associated with olanzapine in children and adolescents but that further studies are necessary to determine the relative risk, magnitude, and time course of antipsychotic-induced weight gain in children and adolescents (Patel et al 2004).

One retrospective study examined the changes in short-term weight and BMI in children and adolescents receiving olanzapine and SEROQUEL. Eligible patients were younger than 18 years, had been admitted to the child and adolescent unit of Austin State Hospital, and had been treated with olanzapine or SEROQUEL (monotherapy) for at least two weeks from October 1997 to October 2001, regardless of diagnosis. Patients were excluded if they had taken any antipsychotic agent within six months before the start of therapy. Fifty patients received treatment with olanzapine and 53 patients received therapy with SEROQUEL. At baseline SEROQUEL treated patients had significantly greater weights and BMIs than those receiving olanzapine (22% of olanzapine patients were considered to be overweight; 49% SEROQUEL patients were considered to be overweight). After correcting for baseline values, increases in weight and BMI were significantly greater in the olanzapine than the SEROQUEL group. The average weight gain and BMI increase in the olanzapine group was 3.8 kg and 1.3 kg/m^2, respectively and the average weight gain in the SEROQUEL group was 0.03 kg and the BMI decreased by 0.2 kg/m^2. The authors concluded that the weight gain and

increases in BMI were more strongly associated with olanzapine in children and adolescents but that further studies are necessary to determine the relative risk, magnitude, and time course of antipsychotic-induced weight gain in children and adolescents (Patel et al 2004).

In summary, the data, along with the medical/scientific literature, do not disclose any significant new safety information about the use of SEROQUEL and weight gain in children.

6.6 Prolonged QT (12 reports)

Medically confirmed reports

There were no medically confirmed reports of prolonged QT in the age groups 0 days to 27 days or 28 days to 23 months. There were two medically confirmed reports of prolonged QT in the two to 11 years age group and five reports in the 12 to 18 years age group. These reports are summarized in Table 58 below. See Appendix B for narratives for these reports.

Table 58 Reports of QT prolongation age 2 to 11 and 12 to 18; medically confirmed (7 reports)

Report #/ Preferred term	Age/ Sex	Dose/ TTO	Medical history	Concomitant medications	PTs/Comments
2003UW01101 Non-serious	Child /?	Dose/ TTO unk	Not provided	Not provided	PTs: ECG QT prolonged. Pt had QT prolongation. Outcome + if Seroquel contd unk. No other info.
2003UW09322 Non-serious	8/M	25 mg/d ay/ 1 year	Anxiety, depression, enuresis, ADHD, bizarre thoughts	Bupropion, desmopressin	PTs: ECG QT prolonged. Pt had prolonged QT (444 msec). Seroquel D/c'd. Pt rec'd (QT=427 msec) about 1 month later. No palpitations, dizziness, syncope, cardiac arrest. No baseline or other info provided.
2004UW02024 non-serious	17/F	200 mg/ day/ TTO unk	Not provided	Not provided	PTs: Electrocardiogram QT corrected interval. Occurred during ECG as routine care. Physician referred Pt to cardiologist who confirmed prolonged QT. Seroquel D/c'd. No outcome or further info.
2003UW05255 serious	12/M	600 mg/ day/ 4 months	ECG QT prolonged	Oxcarbazepine, lithium[a],	PTs: ECG QT corrected interval. Pt had prolonged QT on clonidine in past; clonidine D/c'd. On Seroquel x 4 mos: Pt had prolonged QTc. Seroquel continued. No QTc at baseline, QTc on clonidine, method of correction, or other info reported.

Table 58 Reports of QT prolongation age 2 to 11 and 12 to 18; medically confirmed (7 reports)

Report #/ Preferred term	Age/ Sex	Dose/ TTO	Medical history	Concomitant medications	PTs/Comments
2003UW11369	16/F	300 mg/ day/unk	Overdose while on Seroquel 2 yrs prior, food allergy	Sertraline, buproprion	PTs: ECG QT prolonged, Chest pain. Pt c/o chest pain; an ECG was performed. Prolonged QT identified. No data provided. No treatment or whether Seroquel was cont's provided. No further info provided.
2003GB00456 serious	16/F	175-200 mg/ day/ 17 days	Not provided	Not provided	PTs: ECG QT prolonged[b], palpitations, blood pressure increased, constipation. Had AE 17 days after starting Seroquel + discontinuing risperidone. Seroquel D/c'd. All AEs resolved.
2002UW09570 serious	18/M	??/ TTO unk	Not provided	Valproate semisodium, olanzapine[b], bupropion hydrochloride[b]	PTs: ECG QT prolonged, Dizziness, Medication error. Pt had AEs after snorted and ingested 6-10 Seroquel tabs. Tx: IV, lavage + charcoal. AEs resolved. No further info.

[a] for which ventricular arrhythmia, atrioventricular block, cardiac conduction abnormalities, sinus node dysfunction, bradycardia, and lithium toxicity resulting in QT prolongation or death have been reported,
[b] for which sudden death, Q and T wave distortions, and shock have been reported,
? or unk=unknown, contd.=continued, info=information, ADHD=attention deficit hyperactivity disorder, D/c'd=discontinued.

In the two to 11 years age group, one of the two reports (2003UW09322) described a patient who was taking SEROQUEL for a sleep disorder. The QTc interval during SEROQUEL therapy was 444 msec and one month after SEROQUEL was discontinued was 427 msec; however, neither the method of QT correction nor baseline QTc values was provided. The second report (2003UW01101) contained scant clinical detail (no data provided) and did not lend itself to analysis.

In the 12 to 18 years age group, none of the five reports provided baseline QTc measurements and only one of the five reports (2003UW05255) provided a QTc measurement at the time of the event (although the correction method was not reported). The remaining four reports had no baseline QTc measurements or QTc measurements at the time of the event. The first report (2003UW05255; "Electrocardiogram QT prolonged") was confounded by a concomitant medication (lithium) for which ventricular arrhythmia, atrioventricular block, cardiac conduction abnormalities, sinus node dysfunction, bradycardia, and lithium toxicity resulting in QT prolongation or death have been reported, and a medical history of QTc interval prolongation while on clonidine. Another of the five reports (2002UW09570; "Electrocardiogram QT prolonged") was confounded by a concomitant medication (olanzapine), for which sudden death, Q and T wave distortions, and shock have been reported, and the patient's misuse of SEROQUEL (snorted and ingested 6-10 tablets). The

remaining three reports (2004UW02024; "Electrocardiogram QT prolonged," 2003GB00456; "Electrocardiogram QT prolonged," 2003UW11369; "Electrocardiogram QT prolonged") contained scant clinical detail and did not lend themselves to analysis.

Non-medically confirmed reports

There were no medically unconfirmed reports of prolonged QT in any age group.

Taken together, the post marketing reports were confounded by concomitant medications, or provided insufficient information for clinical analysis. Thus, they do not establish a causal relationship between SEROQUEL and prolonged QT in children.

Clinical trial reports

There were five (all non-serious and all from the same investigator and the same site) reports of "Electrocardiogram abnormal" in the pediatric population of prolonged QT during clinical trials with SEROQUEL. The verbatim terms were as follows: Borderline prolonged QT, Prolonged QT interval, Prolonged QTc, Intraventricular conduction delay, and Borderline QT and QTc interval. No patients were withdrawn from the study due to this event. Four of the events were assessed as causally related to SEROQUEL by the investigator. Three of the patients recovered while SEROQUEL was continued. For the remaining two, the patient's outcome and whether SEROQUEL was continued was unknown. One patient (5077IL/0038/0001/0107) had a baseline QT value of 0.396 and a corrected QT of 0.433. At the time of the event the patient's QTc ranged from 0.433 to 0.464. This patient continued SEROQUEL and recovered. Another patient (5077IL/0038/0001/0102) had a baseline QT value of 0.367 and a QTc of 0.438. At the time of the event the patient's QTc ranged from 0.441 to 0.458. This patient continued SEROQUEL but the outcome of the QT prolongation was unknown. The third patient (5077IL/0038/0001/0104) had a baseline QT value of 0.364 and QTc of 0.417. The patient's QTc at the time of the event ranged from 0.417 to 0.445. The patient continued SEROQUEL and subsequently recovered. Another report (5077IL/0038/0001/0103) had a baseline QT value of 0.40 and a QTc of 0.438. At the time of the event the QTc ranged from 0.43 to 0.472. The patient's outcome and whether SEROQUEL was continued was unknown. The last patient (5077IL/0038/0001/0106), who had a history of AV block, had a baseline QT value of =0.352 and a QTc of 0.438. At the time of the event, the patient's QT at the time of the event was 0.344 to 0.408 and a QTc of 0.423 to 0.448. The patient recovered while SEROQUEL was continued. (For all reports, the method of correction was unknown.)

For the patients with QT values reported, none of them had QT prolongation of clinical importance. In every case where it was known whether the patient continued SEROQUEL or not, SEROQUEL was continued. In the two cases where outcome was provided following continuation of SEROQUEL, the event resolved. Thus, the clinical trial reports do not suggest a causal relationship between QT prolongation and SEROQUEL.

6.7 Tardive dyskinesia (20 reports)

Medically confirmed reports

There were no medically confirmed reports of TD in the age groups 0 days to 27 days or 28 days to 23 months. There were 10 medically confirmed reports of TD in the two to 11 years age group and nine reports in the 12 to 18 years age group.

In the two to 11 years age group, one of the 10 reports (2004UW09544) described a patient who experienced TD after 14 months of SEROQUEL treatment. The dose of SEROQUEL was decreased and the patient recovered one week later. Another report (2002UW16921) was confounded by a concomitant medication (risperidone) for which TD has been reported. SEROQUEL was discontinued (it was unknown if risperidone was continued) and the TD continued. Another report (2003UW07033) described what might have been a withdrawal dyskinesia. The patient discontinued risperidone and started SEROQUEL the next day; four days later the patient experienced TD. Another report (1999UW00525) described a patient who developed TD after six months on SEROQUEL. Both SEROQUEL and valproate were discontinued and the patient recovered. Another patient (2002UW16191) experienced tongue movements (reported as to be TD), which the reporter thought was a symptom of mental retardation. Another report (2003UW06087) contained incomplete information. The patient developed TD after nine months to one year of SEROQUEL treatment. The dose of SEROQUEL was decreased but no outcome was provided. The remaining four reports contained scant clinical detail and did not lend themselves to analysis (2001UW01237, 2001UW15005, 2002UW13474, 2003UW09443).

In the 12 to 18 years age group, one of the nine reports (2003UW05090) described a patient who developed TD after three years of SEROQUEL treatment. SEROQUEL was discontinued and the patient recovered. Four reports described patients who had taken SEROQUEL for less than two months and developed TD (1999AP00178: 40 days, 2002UW09464: one week, 2003UW02377: one month, 2003UW12993: 22 days). One of the four patients (2002UW09464) had rapidly discontinued risperidone treatment within one week of the event, suggesting a possible withdrawal dyskinesia. The remaining four reports contained scant clinical detail and did not lend themselves to analysis (2001UW02639, 2003UW14304, 2003UW15079, 2004UW18926).

Non-medically confirmed reports

There were no medically unconfirmed reports of TD in the 0 days to 27 days, 28 days to 23 months, and two to 11 years age groups. There was one medically unconfirmed reports of TD in the 12 to 18 years age group.

The medically unconfirmed report (2003UW15096) described a 14-year-old patient who according to her mother, experienced TD, severe chest pain, uncontrollable jerking, and blurry vision which "prohibited her from working and attending school because she couldn't read" after about four months of SEROQUEL treatment. Medical history included depression. Concomitant medications included citalopram, estradiol, propranolol, benzatropine, and lorazepam. The patient went to two different emergency rooms. Five days later, the patient

had four spells of severe chest pain that lasted for approximately one to three hours. "The pain was so severe she felt she could not breathe and couldn't do anything except lay down." No outcome or any other information was provided. Despite attempts, no follow up or medical confirmation was received.

Section 4.4 *Special warnings and special precautions for use* of the SEROQUEL CDS states:

> "Tardive Dyskinesia
> In controlled clinical trials, the incidence of EPS was no different from that of placebo across the recommended therapeutic dose range. This predicts that SEROQUEL has less potential than standard antipsychotic agents to induce TD. However, if signs and symptoms of TD appear, dose reduction or discontinuation of SEROQUEL should be considered."

Section 5.1 *Pharmacodynamic properties* of the SEROQUEL CDS states:

> "Pharmacodynamic effects:
> In pre-clinical tests predictive of EPS, quetiapine is unlike standard antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D2 receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D2 receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the A10 mesolimbic but not the A9 nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration. The results of these tests predict that SEROQUEL should have minimal EPS liability, and it has been hypothesised that agents with a lower EPS liability may also have a lower liability to produce tardive dyskinesia."

Assessment of causality was difficult in most of these cases because of either scant clinical detail, less than three months between drug exposure and outcome, or confounding by concomitant medications. (The diagnosis of neuroleptic-induced TD requires a history of the use of neuroleptic medication for at least three months, according to the criteria stated in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (American Psychiatric Association 2000). Following a review of the reports of TD, no significant new safety information was identified regarding the use of SEROQUEL in children and TD. AstraZeneca will continue to review reports of TD as part of its ongoing safety surveillance for SEROQUEL.

Clinical trial reports

There were no reports of TD in the pediatric population during clinical trials with SEROQUEL.

6.8 Extrapyramidal symptoms (91 reports)

Medically confirmed reports

There were no medically confirmed reports of EPS in the age groups 0 days to 27 days or 28 days to 23 months. There were 33 medically confirmed reports of EPS in the two to 11 years age group and 45 reports in the 12 to 18 years age group.

In the two to 11 years age group, one of the 33 reports (2003AP04288) described a patient who experienced EPS after the dose of SEROQUEL was increased. The patient was treated with benztropine and recovered. No information was provided about the patient's concomitant medications, medical history, or if SEROQUEL was continued. Another report (2003UW06318) described a patient who experienced muscle twitching and difficulty breathing after risperidone was discontinued. The patient, who had taken SEROQUEL for an unknown amount of time, was hospitalized. SEROQUEL was discontinued, and the patient recovered. This report contained incomplete information (no medical history, treatment, duration of medications and events), therefore a causal relationship could not be established. Another report (2002UW06262: tic, extrapyramidal disorder) was confounded by the patient's history of tics on risperidone and EPSs prior to starting SEROQUEL (which worsened on SEROQUEL). Another two reports described possible withdrawal dyskinesia. For one of the four reports (1998UW49956), patient's dyskinesia was thought by the physician to be due to the withdrawal of fluphenazine. Another of the two reports (1999UW01944) was confounded by a concomitant medication (lithium) for which dyskinesia has been reported.

Another report (1999UW00525: dyskinesia) was discussed above with the reports of TD. Another report (1999UW04138: tremor) contained incomplete information. It was unclear when SEROQUEL was discontinued in relation to the recovery from the tremor.

Another report (2002UW06808: dystonia) described a patient who experienced dystonia on the day that SEROQUEL was started (which was the day after the last dose of risperidone). SEROQUEL was decreased (400 mg/day to 100 mg/day) but the event did not improve. Patient was treated with diphenhydramine and lorazepam and SEROQUEL was discontinued. The event resolved. It is possible the patient experienced a withdrawal reaction to the discontinuation of risperidone prior to the event. Seven reports were confounded by concomitant medications for which the event or EPS have been reported (2001UW00177: dystonia, sertraline, 2002UW16351: muscle twitching, paroxetine, 2001UW12258: dyskinesia, risperidone, 2002UW14894: tic, dextroamphetamine, EPS, 2003UW16639: tremor, dyskinesia; fluoxetine) 2001UW07141: muscle twitching; gabapentin, 2001UW12261: dystonia; olanzapine). The remaining 17 reports contained scant clinical detail and therefore an assessment of causality was not possible (2002UW12659, 2003UW01918, 2004UW02295, 2004UW12966, 2004UW15270, 2003UW04443, 2002UW14926, 2002UW14868, 2004UW06193, 2002UW12947 (dystonia, dyskinesia), 1999UW03177, 1999UW02175, 2004UW12776, 2003UW14889, 1999AP05664: akathisia, 2001UW11878: dystonia, muscle twitching, 2003UW06962: dystonia, 2000UW04018: dyskinesia).

In the age 12 to 18 years age group, 20 of the 45 reports were confounded by a concomitant medication for which the event and/or EPSs have been reported (2001UW15470: akathisia; chlorpromazine, restlessness, 1998UW45326: dyskinesia; valproate, chorea, 2004UW05154: dyskinesia; bupropion, 1998UW45328: dyskinesia; lithium, 2003SE02715: dystonia; clothiapine, 2002GB01468: dystonia; sertraline, valproate, 2001UW12759: dystonia; sertraline, valproate, 2001UW11258: dystonia; lithium, 2000UW03450: dystonia; olanzapine, venlafaxine, haloperidol, 2000UW00715: dystonia; valproate, 2003UW11925: dystonia; paroxetine, choreoathetosis, 2004UW15310: extrapyramidal disorder; lithium, 2003GB00460: extrapyramidal disorder; haloperidol, 2001UW07886: muscle rigidity; bupropion, 2001UW02955: muscle twitching; risperidone, dyskinesia (2), akinesia, 2003SE00244: akathisia, fluvoxamine, 2003UW09050: akathisia, sertraline, 2002GB01653: cogwheel rigidity, sertraline, valproate, 2004AC00232: extrapyramidal disorder, akathisia, parkinsonism, paroxetine, 2003UW14113: muscle twitching, paroxetine.

The remaining 24 reports contained scant clinical detail and did not lend themselves to analysis (2004UW17908: akathisia, 2003SE05619: akathisia, extrapyramidal disorder, 2003UW11938: bucoglossal syndrome, 2003SE00829: drooling, 2004UW20560: dyskinesia, 2004PK00903: dyskinesia, 1999UW01066: dyskinesia, 2003UW08073: dyskinesia, 2001UW12872: dystonia, 2001UW00734: dystonia, 1999UW00527: dystonia, dyskinesia, 2004UW07711: extrapyramidal disorder, 2004SE04379: extrapyramidal disorder, 2003UW12294: extrapyramidal disorder, 2002GB01559: masked facies, hypokinesia, 2004SE03153: muscle spasms, 2001AP03699: muscle spasms, 2004UW04388: psychomotor hyperactivity, hypertonia, 2002UW07087: restlessness, 2001UW06676: tremor, 2001UW09830: tremor, dyskinesia, 1999UW03979: tremor, dyskinesia, 2001UW14363: dyskinesia, 2003UW15394: nuchal rigidity).

The last report (2003UW16728: dystonia, muscle rigidity) described a patient who took one dose of SEROQUEL (300 mg) and woke up the next morning with neck rigidity, fever, swollen tongue, sore throat, dizziness, increased salivation, and stiff neck. A strep infection was diagnosed, but the physician thought the patient had experienced a "possible dystonic reaction" as well. SEROQUEL was discontinued and the patient recovered within one day. No information was provided regarding concomitant medications the patient may have been receiving.

Assessment of causality was difficult in these cases because of either scant clinical detail, or confounding by concomitant medications and illnesses.

Non-medically confirmed reports

There were no medically unconfirmed reports of EPS in the age groups 0 days to 27 days or 28 days to 23 months. There were six medically unconfirmed reports of EPS in the two to 11 years age group and four reports in the 12 to 18 years age group.

In the age two to 11 years age group, one of the six reports (2003UW02049: dyskinesia) described a patient who experienced dyskinesia after discontinuing risperidone. Therapy with SEROQUEL was then discontinued and the patient recovered on an unknown date. Another

report (2003UW16631: dystonia) was confounded by a concomitant medication (fluvoxamine) for which dystonia has been reported. The remaining four reports (2003UW0352: extrapyramidal disorder, 2001UW06548: dyskinesia, 2003UW10706: muscle twitching, 2000UW01272: tremor) contained scant clinical detail and did not lend itself to analysis.

In the age 12 to 18 years age group, three of the four reports were confounded by concomitant medications for which tremor and/or EPS has been reported (2004UW14965: olanzapine, 2002UW13956: paroxetine, 2004UW20338: valproate). The last report (2004UW06116) described muscle rigidity as a symptom of neuroleptic malignant syndrome.

Assessment of causality was difficult in these reports because of either confounding by concomitant medications known to cause EPS or because of scant clinical detail.

Clinical trial reports

There were three non-serious reports in the pediatric population of EPS (tremor (2), akathesia (1)) during clinical trials with SEROQUEL.

See section 6.7 *Topic of interest; Tardive dyskinesia* above for language in the SEROQUEL CDS regarding EPS. Following a review of all the data for EPS, no significant new safety information was identified regarding the use of SEROQUEL in children and EPS. AstraZeneca will continue to review reports of EPS as part of its ongoing safety surveillance for SEROQUEL

6.9 Cataract (17 reports)

Medically confirmed reports

There were no medically confirmed reports of cataract in the age groups 0 days to 27 days or 28 days to 23 months. There were three medically confirmed reports of cataract in the two to 11 years age group and 12 reports in the 12 to 18 years age group, summarized in Table 59 below. See Appendix B for narratives for these reports.

Of the 15 reports of lens opacities, five patients received baseline eye exams (2001UW01918; 2001UW07040; 2001UW06912; 2004UW01291 and 1999UW00052). Of these five reports, one report (1999UW00052) noted that the baseline exam was "possibly positive," though information concerning the examiner was not provided. Another report (2004UW01291) noted that the patient's baseline exam by one optometrist was normal and the subsequent exam by a different optometrist revealed cataracts; however a third exam by a pediatric ophthalmologist showed no evidence of cataracts. The remaining three reports (20001UW07040; 2001UW06912; 2001UW01918) do not indicate if both eye exams (baseline and at the time of the event) were done by the same examiner.

Five other reports provided incomplete information and it is unknown if a baseline exam was performed (2001UW08694, 2004UW02895, 2003UW11378, 2003UW03542, 2001UW16257).

The remaining five reports described patients who did not have a baseline exam (2000UW01591, 2002UW12495, 2001UW04295, 2004UW08477, 2000UW00840).

Table 59 Reports of Cataracts Age two to 11 years and Age 12 to 18 years (15 reports)

Report #/ Preferred term	Age/ Sex	Dose/ TTO	Medical history	Concomitant medications	PTs/Comments
2000UW01591 Serious	11/F	250 mg/day/ ≈10 weeks	Not provided	Olanzapine, risperidone	PTs: Cataract, Visual acuity reduced. After 2 to 3 mos Pt developed bilateral cataracts. Pt received olanzapine, risperidone, + Seroquel sequentially but not simultaneously. Seroquel D/c'd + risperidone resumed. Exam method not reported. No baseline exam.
2002UW12495 Non-serious	10/F	375 mg/day/ > 8 mos	Not provided	Bupropion	PTs: Cataract, Weight increased. No baseline exam. Pt developed cataract in left eye + significant wt gain. Outcome + if Seroquel contd unk. No other info.
2001UW01918 Non-serious	6/M	50 mg/day/ 6-8 mos	ADHD	Unspecified stimulants	PTs: Vision blurred. Ophthalmologist exam noted hazing in eye. Baseline ophthalmologist exam (unk if same physician) =no abnormalities. Reporter felt this "was not a drug-induced cataract." No other info.
2001UW08694 serious	14/M	600 mg/day/ TTO unk	Not provided	Paroxetine, levothyroxine	PTs: Cataract, Visual field loss. Pt had events while on Seroquel. No further information was provided.
2001UW07040 serious	14/?	Not provided/ ≥3 months	Not provided	Methylphenidate	PTs: Bilateral cataracts. Event observed following 3 months of treatment with Seroquel. No further information was provided
2001UW06912 serious	16/F	650 mg/day/ 22 months	Anaemia, enuresis, reflux oesophagitis, impulse-control dis, obesity, seborrhoeic dermatitis, convulsion, mental retardation, incompetent mitral valve, constipation	Lithium, diazepam, lorazepam, donnatal, famotidine, naproxen, alumina/magnesia/simethicone, docusate, aluminum/ magnesium	PTs: Cataract. Event observed after ~22 months of Seroquel. No prior hx of cataract. Pt. was on many concomitant meds. D/c'd Seroquel; was being switched to ziprasidone.
2001UW04295 serious	12/F	300 mg/day/ 3-6 months	Mental retardation severity unspecified, head banging	Diphenhydramine, hydroxyzine, chlorpromazine[a], loxapine	PTs: Posterior capsule opacification. Event after 3-6 months of Seroquel. Pt was on multiple con meds and had a hx of head banging. No further information was provided

Table 59 Reports of Cataracts Age two to 11 years and Age 12 to 18 years (15 reports)

Report #/ Preferred term	Age/ Sex	Dose/ TTO	Medical history	Concomitant medications	PTs/Comments
2004UW08477 non-serious	17/F	450 mg/day/ 2 months after tx stopped	Post-traumatic stress dis, sexual abuse victim, attention deficit/ hyperactivity dis, overdose, mental retardation , depression	Citalopram, gabapentin	PTs: Cataract. Discovered 2 months after Seroquel D/c'd. No baseline information was provided. Condition may have predated Seroquel use.
2004UW02895 non-serious	??/?	??; TTO unk	Not provided	Not provided	PTs: Cataract. Scant report. Pt. had cataracts after starting Seroquel. No further information provided.
2004UW01291 non-serious	12/M	100 mg/day; 2 months	Hypothyroidism, drug hypersensitivity	Lithium, valproate, levothyroxine, risperidone[a], benztropine	PT: Bilateral cortical cataracts. Event after 2 months of Seroquel. Normal baseline exam. Pt. was adopted and family hx unk. Outcome: Follow up information from a pediatric ophthalmologist stated the patient did not have cataracts.
2003UW11378 non-serious	14/M	??; TTO unk	Not provided	Not provided	PTs: Cataract[a]. Scant report.
2003UW03542 non-serious	16/F	??; TTO unk	Not provided	Fluoxetine	PTs: Cataract cortical[a], Cataract subcapsular[a]. Detected during ongoing Seroquel and fluoxetine (dose unk) therapy. Physician believed cataracts to be congenital.
2001UW16257 non-serious	??/M	??; ~1 yr	Mental retardation severity unspecified	Not provided	PT: Cataract. Scant report. Pt diagnosed with cataracts after approximately 1 year of Seroquel.
2000UW00840 non-serious	15/M	100 mg/day; 10 months	Attention deficit/ hyperactivity dis, depression	Methylphenidate, fluoxetine	PT: Lenticular opacities. Detected approximately 10 months after Pt started Seroquel. Seroquel continued. 2 months later: exam revealed no evidence of cataracts.
1999UW00052 non-serious	14/F	250 mg/day; 6 months	Attention deficit/ hyperactivity dis, depression, possible maternal hx of eye disease	Methylphenidate, amitriptyline	PTs: Bilateral cataracts, Blurred vision. Events after 6 months of Seroquel. Lenticular opacities were found which might have predated Seroquel. Outcome: Pt rec'd.

[a] for which corneal and lens opacities have been reported, ? = unknown, w/ = with, rec'd = recovered, tx = treatment, unk = unknown, hx = history, mo(s)=month(s), D/c'd=discontinued, wt=weight, info=information, ADHD=attention deficit hyperactivity disorder.

In the two to 11 years age group, one of the three reports (2000UW01591) described a patient who received SEROQUEL for 10 weeks. According to an independent ophthalmologist, the lens is slowly responsive to cataractogenic toxicity and cataract formation attributed to drug therapy requires a minimum of six months of drug exposure. Thus, it is unlikely this patient's cataract was caused by SEROQUEL. The second report (2002UW12495) described a patient who had previously been treated with carbamazepine (for which lenticular opacities have been reported). Additionally, no baseline eye exam was performed and no medical history was provided. The third report (2001UW01918) described a patient who was found to have hazing in the eye. The reporter/ophthalmologist assessed this as not "a drug-induced cataract," as it was unclear in this report if the patient experienced a cataract at all.

In the 12 to 18 years age group, one report (2001UW06912) of a cortical and peripheral cataract in a patient taking multiple concomitant medications was assessed by an independent ophthalmologist as not related to SEROQUEL treatment. The independent ophthalmologist commented that a "cortical and peripheral" cataract at age 16 most often is congenital. Another report (2001UW04295) was confounded by the medical history of head banging. Penetrating or blunt trauma is a common cause of cataracts in older children (Fallaha 2001, Foster 1997). In addition, this report was confounded by a concomitant medication (chlorpromazine) for which lens and corneal deposits and cataract has been reported. For another report (2004UW01291) follow up information was received from a pediatric ophthalmologist, which stated that the patient did not have cataracts.

For another report (2004UW08477) it was possible that the condition existed prior to the use of SEROQUEL. Another report (2001UW08694) described a patient who had "small cataracts" with substantial visual field loss. An ophthalmologist examined the patient however the results were not available. "Small cataracts" cannot explain profound loss of visual field as reported for this patient. The report was confounded by a concomitant medication (paroxetine) for which cataract has been reported. SEROQUEL was continued. An independent expert in ophthalmology reviewed this report and advised a formal neurological exam be performed for this patient.

Another report (2000UW00840) contained a report of lens opacity after an eye exam by an optometrist. However, a follow up exam by an ophthalmologist showed no evidence of cataracts. Another report (2003UW03542) described a patient with both cortical and posterior subcapsular cataract. The reporter/ophthalmologist believed the opacity to be congenital in origin. It was not reported if the cataract was unilateral or bilateral and no information was provided on the dose and duration of SEROQUEL exposure.

Another report (1999UW00052) was confounded by the patient's medical history, which included lenticular opacities, which may have predated SEROQUEL use.

Another report (2001UW07040) described a patient who developed bilateral cataracts and lens changes following three months of SEROQUEL treatment. According to an independent ophthalmologist, the lens is slowly responsive to cataractogenic toxicity and cataract formation attributed to drug therapy requires a minimum of six months of drug exposure.

Thus, it is unlikely this patient's cataract was caused by SEROQUEL. No further information was provided.

Another three reports (2004UW02895, 2003UW11378, 2001UW16257) contained scant clinical detail and did not lend themselves to analysis.

These reports were confounded by concomitant medications or medical history, or described insufficient drug exposure time, or provided insufficient information for clinical analysis. Thus, they do not establish a causal relationship between cataract and SEROQUEL use in children. They provide no significant new safety information as to the known safety profile for SEROQUEL.

Clinical trial reports

There were no reports of cataract in pediatric patients participating in clinical trials with SEROQUEL.

Non-medically confirmed reports

There were no medically unconfirmed reports of cataract in the age groups 0 days to 27 days, 28 days to 23 months, or the two to 11 years age groups. There were two medically unconfirmed reports of cataract in the 12 to 18 years age group.

In the 12 to 18 years age group, both of the reports (2002UW10010, 2002UW07307) contained scant clinical detail and did not lend themselves to analysis.

Summary for cataract

Characteristics of drug-induced lens toxicity are uniformity of type of opacity and of location within the lens, plus a relationship to dose and duration of exposure. These characteristics are lacking in these reports. Following a review of all the pediatric data, an independent ophthalmologist concluded that SEROQUEL had no consistent, uniform, biologically plausible, bilateral, dose- or duration-related effect on the lens. The independent ophthalmologist concluded that there is no discernible pattern in the pediatric reports, as no two reports were alike. No single report in this cohort presented with a clearly documented finding typical of lens toxicity. Thus, the post-marketing and pediatric clinical trial data do not establish a causal association between the administration of SEROQUEL and the development of cataract in children. Following a review of all the data, no significant new safety issue regarding the use of SEROQUEL in the pediatric population was identified.

6.10 Neonatal Drug Withdrawal (10 reports)

Medically confirmed reports

In the age 0 days to 27 days, 10 reports described neonatal drug withdrawal syndrome. Of these 10 reports, eight were confounded by concomitant medications taken by the mother, for which neonatal withdrawal has been reported (2003UW13923: paroxetine; 2004AP01045: diazepam, also oxprenolol for which neonatal respiratory distress and jaundice have been reported; 2002GB02278: paroxetine; 2002GB02909: diazepam, fluoxetine; 2003SE05724:

venlafaxine; 2001UW01690: paroxetine, 2003GB01471: lorazepam, and 2001AP03788: diazepam, venlafaxine). In addition, four of these eight reports were also confounded by maternal medical history (2003SE05724: cigarette smoking during pregnancy, DM, prior alcohol abuse; 2004AP01045: drug overdose with valproate during pregnancy; 2003GB01471: medical history of two suicide attempts during pregnancy, 2001AP03788: history of opiate and benzodiazepine dependence). The two remaining reports (2003AP03328; 2004UW03627) contained minimal information and thus provided inadequate information to attribute causality to SEROQUEL. Assessment of causality was difficult in these reports because of either confounding by concomitant medications known to cause neonatal withdrawal or because of scant clinical detail.

No other reports of neonatal drug withdrawal were received for any other age group.

Non-medically confirmed reports.

There were no non-medically confirmed reports of neonatal withdrawal received for any age group.

Clinical trial reports

There were no reports in the pediatric population of neonatal withdrawal during clinical trials with SEROQUEL.

Following a review of the reports, it was determined that the data do not establish a causal relationship between SEROQUEL and neonatal withdrawal. AstraZeneca will continue to keep reports of neonatal withdrawal under careful review.

6.11 Hyperprolactinemia and related adverse events (35 reports)

Medically confirmed reports

There were no medically confirmed reports of hyperprolactinemia and related AEs in the age groups 0 days to 27 days or 28 days to 23 months. There were three medically confirmed reports of hyperprolactinemia and/or related AEs in the two to 11 years age group and 29 reports in the 12 to 18 years age group.

In the two to 11 years age group, one of the three reports (2003UW03532: galactorrhea) was confounded by a concomitant medication (valproate) for which hyperprolactinemia has been reported. The other two reports (2003UW06694: abnormal hair growth, 2001UW11378: gynecomastia) contained scant clinical detail and did not lend themselves to analysis.

In the 12 to 18 years age group, one report (2001GB00216) described a female patient who began lactating after two days of therapy with SEROQUEL. The patient had previously taken risperidone and also experienced lactation at that time. The patient had no obvious prolactin problems but further investigations were planned. SEROQUEL was discontinued two months later and the patient recovered. Therapy with clozapine was initiated and the patient developed severe neutropenia, so clozapine was discontinued. SEROQUEL was reintroduced and the patient began lactating again without elevated prolactin levels. SEROQUEL was

again discontinued and the event resolved. No information was provided regarding the patient's medical history, concomitant medications, or prolactin levels. Another report (2002GB02051) described a patient who experienced hyperprolactinemia (prolactin=1148 mu/L) after two weeks of SEROQUEL. No baseline prolactin levels were provided. The patient had been receiving risperidone for one month (for which hyperprolactinemia, has been reported) immediately prior to SEROQUEL, but had discontinued risperidone because of neutropenia and EPS. It was unknown if SEROQUEL was continued. The patient had not yet recovered at the time of the report.

One report of erectile dysfunction (2003UW05543) was confounded by the patient's history of erectile dysfunction and anticipatory anxiety while using an unspecified antidepressant. Another 16 reports, which were confounded by concomitant medications, are contained in Table 60 below.

Table 60 Reports confounded by concomitant medications (16 reports)

Report #	PT	Confounding medication	AEs reported for med
1998AP46145	Amenorrhea	Levonorgestrel	Altered menstrual cycles/irregular menstrual bleeding
		Citalopram	Hyperprolactinemia
2001UW14772	Amennorhea Blood prolactin ↑	Sertraline	Hyperprolactinemia
2002UW06418	Blood prolactin ↑	Risperidone	Hyperprolactinemia
2003GB02687	Hyperprolactinemia	Sertraline	Hyperprolactinemia
2002UW05722	Hyperprolactinemia	Chlorpromazine	Galactorrhea (Pt was reported to be lactating)
2001AP05884	Blood prolactin ↑	Sulpiride	Altered prolactin secretion
2003SE03267	Galactorrhea	Risperidone	Galactorrhea, hyperprolactinemia
2000UW00527	Galactorrhea	Risperidone	Galactorrhea, hyperprolactinemia
2002AP01918	Galactorrhea	Fluoxetine	Hyperprolactinemia, galactorrhea
2003UW13356	Galactorrhea	Fluoxetine	Hyperprolactinemia, galactorrhea
2003UW13928	Galactorrhea	Sertraline	Hyperprolactinemia, galactorrhea
2002GB00510	Gynecomastia	Amisulpiride	Hyperprolactinemia resulting in gynecomastia
2002UW10092	Gynecomastia	Valproate	Gynecomastia
2003UW12830	Gynecomastia	Oxcarbazepine	Gynecomastia
2004UW16917	Gynecomastia	Olanzapine	Hyperprolactinemia
2002UW10093	Breast swelling	Valproate	Gynecomastia
		Clonidine	Gynecomastia

The remaining 10 reports contained scant clinical detail and did not lend themselves to analysis (2003UW07731: galactorrhea, 2004UW02051: blood prolactin increased,

2004GB02982: libido increased, 2001UW12390: breast discharge, 2004UW18591: galactorrhea, 2003UW11076: hyperprolactinemia, 2003SE02712: hyperprolactinemia, 2002SE04469: gynecomastia, 2002UW13388: blood testosterone decreased, 2003GB00748: blood prolactin increased).

Only six of the 29 reports provided prolactin levels at the time of the event, however baseline prolactin levels or recovery/follow-up prolactin levels were not provided for these six reports. For the sake of completeness, some of the AEs discussed in this section (eg, amenorrhea, erectile dysfunction) may or may not have been caused by hyperprolactinemia. In the absence of prolactin levels, it is difficult to attribute such events to hyperprolactinemia. Therefore, taken together, assessment of causality was difficult in these cases because of limited information, confounding by medical history or concomitant medications, unclear temporal sequence of exposure and outcome, or scant clinical detail. Thus, these reports do not establish a causal relationship between hyperprolactinemia and related AEs and SEROQUEL.

The *Pharmacodynamic* properties section 5.1 of the SEROQUEL CDS states:

> "Unlike many other antipsychotics, SEROQUEL does not produce sustained elevations in prolactin, which is considered a feature of atypical agents. In a multiple fixed-dose clinical trial, there were no differences in prolactin levels at study completion, for SEROQUEL across the recommended dose range, and placebo."

Non-medically confirmed reports

There were no medically unconfirmed reports of hyperprolactinemia and related AEs in the 0 days to 27 days, 28 days to 23 months, and two to 11 year age group. There were two medically unconfirmed reports of hyperprolactinemia and related AEs in the 12 to 18 years age group. One report (2004SE03105) described a patient who experienced amenorrhea and breast discharge. The other report (1999UW03534) described a patient who experienced breast discharge. Both of these reports contained scant clinical detail and did not lend themselves to analysis.

Clinical trial reports

There was one report (5077IL/0038/0001/0106) in the pediatric population of hyperprolactinemia during clinical trials with SEROQUEL. This non-serious event was assessed as non-related by the investigator.

Literature

The only relevant literature was an abstract (Saito et al 2004), which presented preliminary data from an ongoing study, which compared changes in prolactin levels in children and adolescents after treatment with risperidone, olanzapine, or SEROQUEL. Prolactin levels were obtained at baseline and after a mean of 11.2 weeks from 40 subjects (risperidone=21 patients, olanzapine=13 patients, SEROQUEL=6 patients). It was reported that endpoint prolactin levels were significantly higher with risperidone compared to olanzapine or

SEROQUEL; however, no prolactin levels were provided. One of the caveats of this study is the small sample size (n=6) for SEROQUEL. While it was reported that 25% of the subjects experienced sexual side effects at endpoint, which were independent of prolactin levels and treatment groups, no other information about these changes were provided. Therefore, no conclusion can be drawn from this study.

In summary, these data, including the medical/scientific literature, do not establish a causal relationship between SEROQUEL and hyperprolactinemia and related AEs in children. AstraZeneca will continue to keep reports of hyperprolactinemia and related AEs under careful review.

6.12 Stevens Johnson Syndrome (1 report)

Medically confirmed reports

There were no medically confirmed reports of Stevens Johnson Syndrome (SJS) in the age groups 0 days to 27 days, 28 days to 23 months, and 12 to 18 years age group. There was one medically confirmed report of SJS in the two to 11 years age group

1999UW02930: This serious report of "Stevens-Johnson syndrome" described a 9-year-old male patient who was receiving SERQOUEL (175 mg/day; 8 days) for the treatment of attention deficit hyperactivity disorder. Medical history included opposition defiance disorder, seizure disorder, bipolar disorder, and allergies to diphenhydramine, valproate, and haloperidol. Concomitant medications included phenytoin (for which SJS has been reported), nefazodone, and lithium. On Day eight of therapy with SEROQUEL and Day 17 of therapy with phenytoin the patient developed a rash. The next day the rash worsened but improved the next day. All medications were discontinued at this time. The next day the rash worsened with fever and the following day the patient developed erythematous wheals and was transferred the next day to a burn unit with possible SJS. Four days before the rash occurred the patient's phenytoin level was 16.8 (within normal range). The patient was reported to be recovering. No other information was available. Assessment of causality in this report was difficult due to confounding by a concomitant medication for which SJS has been reported.

Non-medically confirmed reports

There were no non-medically confirmed reports of SJS received.

Clinical trial reports

There were no reports in the pediatric population of SJS during clinical trials with SEROQUEL.

The data do not suggest that a causal relationship between SEROQUEL use in the pediatric population and SJS exists.

6.13 Behavioural disturbances (65 reports)

There were three medically confirmed reports of neonatal agitation and one report of irritability in the age groups 0 days to 27 days or 28 days to 23 months. These reports in this age group suggest a nervous system disorder rather than a behavioral disturbance; therefore these reports will not be discussed further in this section. There were 18 medically confirmed reports (23 events; 9: aggression, 2: anger, 2: hostility, 8: agitation, 1: irritability, 1; abnormal behavior) of behavioral disturbances in the two to 11 years age group and 22 reports (25 events; 7: aggression, 10: agitation, 1: irritability, 1: hostility; 6: abnormal behavior) in the 12 to 18 years age group.

In the two to 11 years age group, two reports were confounded by medical history (1998UW43327: aggression, history of mood swings, 2004UW15815: aggression/agitation, history of autism). One report of agitation (2004UW01647) was confounded by a concomitant medication (risperidone) for which agitation has been reported. One report (2004UW14830: anger) described a patient who experienced anger after three days of taking SEROQUEL from a new refill. The patient was given a new lot of SEROQUEL and the event resolved. Another report (2002AP02020: agitation) described an 11-year-old patient who took 1300 mg of her mother's SEROQUEL. The child became somnolent and was hospitalized. Three hours post ingestion the patient became agitated and was treated with lorazepam. Sixteen hours post ingestion the child completely recovered. It is possible that the child's agitation could have been due to strange surroundings. The remaining 13 reports (2000UW04125: aggression/hostility, 2001UW03757: aggression, 2001UW01808: aggression, 2001UW01740: aggression, 2001UW10765: aggression/hostility, 2000UW05082: aggression, 2004UW18888: anger, 2001AP00341: agitation, 2001UW04812: aggression/agitation, 2001UW07141: agitation, 2002GB02905: agitation, 2002UW16351: agitation, 1999AP05604: irritability/abnormal behavior) contained scant clinical detail and did not lend themselves to analysis. One of these patients (2000UW04125) was also taking carbamazepine for which psychosis has been reported.

In the 12 through 18 years age group, one report (2004UW17956: "Aggression," "Agitation") described a patient who had been receiving SEROQUEL for about one year. The patient commenced therapy with nizatidine and within two days experienced aggression and agitation. Nizatidine was discontinued. The patient's father subsequently discovered that the patient had taken the wrong dose of SEROQUEL (50 mg instead of 250 to 300 mg). The patient's symptoms abated. However when nizatidine was reintroduced the patient's symptoms returned and were noted to be worse than previously. Therapy with both SEROQUEL and nizatidine was continued and the patient's outcome was unknown. Another report (2002UW08404; "Aggression") was confounded by concomitant medication (modafinil) for which aggressive tendencies have been reported. No information about the outcome or whether SEROQUEL was continued or not, was provided. Another four reports containing the preferred term "Agitation" were confounded by concomitant medications for which agitation has been reported (2003UW09050: sertraline, 2001UW07886: bupropion, 2000UW03962: paroxetine, haloperidol). One of these four reports (2000UW03962) described a patient who was found dead three days after SEROQUEL treatment began. The patient had a medical history of cardiac arrhythmia and was being treated with propranolol.

The patient failed to take the propranolol for the three days prior to her death, which was believed by the pathologist to be the cause of death.

Another report (1999AP00781; "Aggression") was confounded by the patient's history of aggression. Four reports contained limited information about the event (agitation/aggression) and therefore a causal relationship could not be established. Two of these four reports described patients who took overdoses of SEROQUEL and experienced agitation (2004AC00231; "Agitation," 2003AP01203; "Agitation). Another of the four reports (2002UW13817; "Aggression") described a patient who attempted suicide by ingesting unknown quantities of both SEROQUEL and olanzapine (it was unknown if the patient had been prescribed these medications), slit his wrists, and stabbed his stepfather. The fourth report (1998UW43600; "Aggression") described a patient with a history of autism and mental retardation that exhibited increased aggressive behavior.

Another two reports (2003UW16254, 2004UW15424; both "Abnormal behavior") it was unclear what type of behavioral disturbance the patient was experiencing. The remaining 10 reports contained scant clinical detail and did not lend themselves to analysis (2003UW11552; "Aggression," 2000UW04135; "Aggression," "Hostility," 2003UW09780; "Agitation," 2003UW08574; "Agitation," 2003UW00640; "Agitation," 2001UW01851; "Agitation," 2003GB03350; "Irritability," 2001UW03225; "Abnormal behavior," 2001UW10062; "Abnormal behavior," 2004UW03555; "Abnormal behavior").

Medically unconfirmed reports

There were no medically unconfirmed reports of behavioral disturbances in the age groups 0 days to 27 days or 28 days to 23 months. There were six medically unconfirmed reports (8 events; 3: aggression, 2: hostility, 3: agitation) of behavioral disturbances in the two to 11 years age group and 11 reports (12 events; 2: aggression, 1: anger, 1: irritability, 1: hostility, 7: abnormal behavior) in the 12 to 18 years age group.

In the two to 11 years age group, one report (1999UW04374; "Aggression") was confounded by two concomitant medications (clonidine, dexamphetamine) for which aggression has been reported. Another report (2003UW02049: "Agitation") contained incomplete information. Therapy with SEROQUEL was discontinued, however it was unknown if the patient recovered from the agitation. In addition, no information about the patient's medical history was provided. The other four reports contained scant clinical detail and did not lend themselves to analysis (2002UW06190; "Aggression," 2001UW14903; "Hostility," 2004UW00979; "Agitation," "Hostility," 2003UW11338; "Agitation," "Aggression").

In the 12 through 18 years age group, one report (2003UW10305; "Abnormal behavior") was confounded by the patient's history of mood swings. Another report (2004UW17467; "Aggression") was confounded by a concomitant medication (valproate) for which aggression has been reported. Another report (2003UW02268; "Abnormal behavior") was confounded by a concomitant medication (topiramate) for which behavioral problems have been reported. Another report (2000UW03254; "Irritability") was confounded by a concomitant medication (citalopram) for which agitation has been reported. The remaining seven reports

(2000UW04354; "Anger," 2002UW02601; "Aggression," "Hostility," 2002UW02386; "Abnormal behavior," 2002UW02387; "Abnormal behavior," 2002UW02389; "Abnormal behavior," 2004AP02370; "Abnormal behavior," 2003UW01166; "Abnormal behavior") contained scant clinical detail and did not lend themselves to analysis.

Clinical trial reports

There were four reports of behavior and social disturbances received during clinical trials with SEROQUEL. The first report (2001SE06512; "Aggression") was confounded by a history of conduct disorder and a concomitant medication (chlorazepate) for which rage and aggressive behavior have been reported. The second report (2002SE01290; "Aggression") was confounded by a history of aggressive behavior and a concomitant medication (sertraline) for which aggressive behavior and delusions have been reported. The third report (2003SE00175; "Aggression") was confounded by alcohol and cannabis abuse as well as non-compliance with SEROQUEL regimen. The fourth report (2001UW08245; "Hostility") had no obvious confounding factors but the investigator reported that a longer overlap between the tapering of olanzapine and the upward titration of SEROQUEL might have prevented the hospitalization for hostility.

Following a review of all the data, it was determined that the data do not suggest that a causal relationship between the use of SEROQUEL in the pediatric population and behavioural disturbances exists.

6.14 Overdose (26 reports)

Medically confirmed

There were no medically confirmed reports of overdose in the age groups 0 days to 27 days or 28 days to 23 months. In the age two through 11 years group, four serious reports of overdose ("Intentional overdose" [1], "Overdose" [3]) were received. In the age 12 to 18 years age group, 15 reports (14 serious/1 non-serious) of overdose were received ("Intentional overdose" [3], "Accidental overdose" [1], "Overdose" [11]).

Ages 2 through 11; Monotherapy overdose

Three of these four reports involved an overdose of SEROQUEL alone and were taken by children who were not prescribed SEROQUEL. One of the children (1995AP08538) was a six-year-old who took a 600 mg dose of a relative's SEROQUEL. The child experienced sedation, was hospitalized, and fully recovered the next day. Another report (2002AP02020) described an 11-year-old girl who took 1300 mg of her mother's SEROQUEL and became somnolent. She recovered from the somnolence three hours after ingesting the SEROQUEL and then became agitated and combative. The child was treated with lorazepam and 16 hours post-ingestion had fully recovered. The third report (2004AC00397) described a 2-year-old child who was forcibly given an unknown amount of SEROQUEL by his mother and was found dead. The patient's cause of death was determined upon autopsy to be manual smothering with evidence of prior forced administration of SEROQUEL. Toxicological examination revealed the following: quetiapine concentration=106 mg/L from the femoral vein, 165 mg recovered from the stomach contents, and 760 mg recovered from the

oropharynx. This report is discussed in section 6.1 *Topic of Interest; Reports with an outcome of death.*

Somnolence is listed in the SEROQUEL CDS. Following a review of these reports, no significant new safety information about SEROQUEL and the pediatric population was identified.

Ages 2 through 11; Multi-drug overdose

The fourth report (2000UW03156) described a 6-year-old patient who was receiving SEROQUEL for treatment of ADHD. The patient took 1500 mg of SEROQUEL and one 25 mg dose of thioridazine belonging to his parent. He subsequently experienced lethargy and respiratory distress. The patient was intubated but not ventilated and airlifted to a medical center and treated with epinephrine and dexamethasone (reason unspecified). The following day the patient experienced seizures. The patient was discharged from the hospital four days later fully recovered.

Ages 12 through 18; Monotherapy overdose

Ten of these reports described patients who took an overdose of SEROQUEL alone. Three of these patients were not prescribed SEROQUEL. One of these reports (2001AP00830) is discussed in section 6.3 *Topic of Interest; Suicide.* The other (2004AC00231) was a 15-year-old who took an overdose of her mother's SEROQUEL (dose unknown). She became agitated and confused and was treated with midazolam. Blood work and EKG were normal and quetiapine level 24 hours post ingestion was 804 ng/ml. She remained in the ICU with altered mental status, mumbled speech, normal pupils, dry axilla, hallucinations, and tachycardia. Sixty hours after ingestion physostigmine was given for suspected antimuscarinic manifestations. The patient's speech immediately became clear, sensorium returned to baseline, and she became aware of her current situation. Her quetiapine level at this time was 164 ng/ml. The patient fully recovered on an unknown date. The third report (2003AP01203) described a 15-year-old female who took 1250 mg of a relative's SEROQUEL in a suicide attempt. The patient experienced lethargy, hypotension, and tachycardia, which are listed in the SEROQUEL CDS. This patient also became agitated after arrival to the emergency room, which could have been due to the surroundings and/or resistance to treatment.

In another report (2003UW02945) it was unclear if the patient was prescribed SEROQUEL. This patient took an overdose of SEROQUEL and unknown amount of time later developed a rash. The patient's outcome was unknown.

The remaining six reports described patients who were prescribed SEROQUEL. One of these patients (2004UW03645) took 6 grams of SEROQUEL and was treated with activated charcoal. No AEs were reported and the patient recovered. Four other patients took overdose of SEROQUEL and experienced AEs that are consistent with the safety profile of SEROQUEL overdose (2004UW18692: 900 mg, tachycardia, decreased level of consciousness, hypotension; 1999AP02940: 1250 mg, somnolence; 2004UW07175: 9 grams, coma, convulsion; 1998UW43530: amount unknown, tachycardia). One of these patients (1999AP02940) recovered the next day and the outcomes for the other three patients were

unknown (2004UW18692, 2004UW07175, 1998UW43530). One other patient (2004AP04794) took 2 grams of SEROQUEL and became comatose. The patient remained in a coma for four to six days. She subsequently developed pneumonia, dehydration, and loss of appetite and remained hospitalized for two weeks. The patient's outcome was unknown.

Ages 12 through 18; Multi-drug overdose

The remaining five reports described patients who took multi-drug overdoses (including SEROQUEL). Due to the nature of these reports a causal relationship cannot be determined (2003UW10892: see section 6.1 *Topic of Interest; Reports with an outcome of death*, 2003UW05590, 2002UW13817: see section 6.3 *Topic of Interest; Suicide*, 2004AP01560: section 6.3 *Topic of Interest; Suicide,* 2003UW13081).

Medically unconfirmed reports

There were no medically unconfirmed reports of overdose in the age groups 0 days to 27 days or 28 days to 23 months. In the age two through 11 years group, three serious reports of overdose ("Accidental overdose" [3]) were received. In the age 12 to 18 years age group, four reports containing the preferred term "Overdose" were received.

Ages 2 through 11; Monotherapy overdose

One newspaper report described three children (2004SE03695, 2004SE03694, 2004SE03690) who mistook SEROQUEL for candy and took 19 tablets that were prescribed to one of the children's mother. One child (2004SE03695) experienced convulsions and the other two children (2004SE03694, 2004SE03690) experienced convulsion and coma. The children were hospitalized and fully recovered the next day. Both convulsion and coma with overdose are listed in the SEROQUEL CDS.

Ages 2 through 11; Multi-drug overdose

There were no reports of multi-drug overdose received in this age group.

Ages 12 to 18; Monotherapy overdose

One newspaper article described three teenage girls (2002UW02389, 2002UW02387, 2002UW02386) who experienced a possible overdose of SEROQUEL. All three of them were reported to be behaving oddly. The outcomes of these patients were unknown. One other report (2001UW04156) described a patient who overdosed on 7 grams of SEROQUEL. The patient was treated with activated charcoal. No AEs were reported in relation to the overdose. The patient's outcome was unknown.

Ages 12 to 18; Multi-drug overdose

There were no reports of multi-drug overdose received in this age group.

Clinical trial reports

There were no reports in the pediatric population of overdose during clinical trials with SEROQUEL.

Summary of reports

The *Overdose* section 4.9 of the SEROQUEL CDS states:

> "In clinical trials, experience with SEROQUEL in overdosage is limited. Estimated doses of up to 20 g of SEROQUEL have been taken; no fatalities were reported and patients recovered without sequelae. In postmarketing experience, there have been very rare reports of overdose of SEROQUEL alone resulting in death or coma.
>
> In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e. drowsiness and sedation, tachycardia and hypotension..."

Therefore, these reports provide no significant new safety information about overdose of SEROQUEL in children.

6.15 Status epilepticus (1 report)

Medically confirmed reports

There were no medically confirmed reports of status epilepticus in the age groups 0 days to 27 days, 28 days to 23 months, or two to 11 years. There was one medically confirmed report of status epilepticus in the 12 to 18 years age group.

This serious report (2000UW00205) of "Status epilepticus," "Coma," "Intracranial pressure increased," "Brain oedema," "Brain herniation," "Metabolic acidosis," "Hypokalemia," "Hepatitis," "Ammonia increased," "Activated partial thromboplastin time prolonged," "International normalized ration increased," "Body temperature increased," "Head banging," "Insomnia," "Depression," and "Facial bones fracture" described a 15-year-old male patient who was receiving SEROQUEL (800 mg/day; two months) for the treatment of mania. Medical history included grand mal seizures, autism, depression, behavior disorder, head banging, and insomnia. Concomitant medications included topiramate (and mirtazapine. The patient was started on therapy with SEROQUEL (50 mg/day) due to symptoms of mania. About one month later the patient had a severe head-banging episode and insomnia so the dose of SEROQUEL was increased to 800 mg/day. A few weeks later the patient banged his head, fractured his nose, and developed a left-sided focal seizure that generalized to become status epilepticus. The patient was taken to the emergency room where he was treated with intravenous doses of fosphenytoin, midazolam, and lorazepam. The status epilepticus was reported to have lasted about 45 minutes. A computed tomography (CT) scan showed no evidence of intracranial trauma. The patient was intubated and went into a coma. The coma was attributed to the post-ictal state and the sedatives/hypnotics given as treatment. The patient was started on phenytoin (for which toxic hepatitis and fatal hepatic necrosis have been reported) and the dose of topiramate was increased. Twenty-two hours after the event the patient's one pupil became dilated and fixed (the patient had been extubated two hours previously). Partial cerebral herniation was suspected. The patient's intracranial pressure was not being monitored, however the patient was treated with mannitol and hyperventilation. Blood gases showed a pH of 7.1 and hypokalemia. The patient's ammonia level was elevated

to 70 and his INR and APTT were increased (no values provided). An ECG was abnormal but did not show status epilepticus. A CT scan showed mild cerebral edema following treatment. Two hours after the herniation the patient developed a fever of 102°F, at this time his ammonia was 56. Liver function tests later showed signs of hepatitis with both the AST and ALT being elevated greater than three times normal (no values provided). SEROQUEL, mirtazapine, and phenytoin were discontinued. A magnetic resonance image (MRI) showed hypodensity in a small area of the posterior corpus callosum. At the time of the report the patient was receiving topiramate for seizures, intravenous diazepam and morphine for agitation and was being empirically treated with acyclovir and ceftriaxone for possible infection. It was reported that the patient's elevated ammonia and LFTs normalized shortly after the herniation. The patient was reported to be recovering from all events.

This report was confounded by the patient's history of seizures and head banging, the patient's head banging episode immediately prior to the event, and the subsequent brain herniation (even though the herniation did not become apparent until later).

Medically unconfirmed reports

There were no medically unconfirmed reports of status epilepticus in any age group.

Clinical trial reports

There were no reports of status epilepticus received for patients in clinical trials with SEROQUEL.

Summary

Following a review of this data, it was determined that the data do not establish a causal relationship between the use of SEROQUEL in children and status epilepticus.

7. EVENTS REPORTED ONLY AT THE SECONDARY PREFERRED TERM LEVEL

All cases were manually reviewed for this review including AEs, which were not reported as the primary event (secondary preferred terms). See Appendix C for a list of all events contained in all 840 pediatric postmarketing reports received by AstraZeneca for SEROQUEL. In the review of reports by age group, many of the events reported at a secondary level were reviewed when cases containing the same event at the primary level were reviewed. For Topics of interest, all related events were reviewed regardless of whether the event was reported first (primary preferred term) or after the first event in a case (secondary preferred term). The remaining secondary preferred terms (those not discussed under topics identify by reports containing primary preferred terms of the same topic, or not a Topic of interest) were reviewed for this section. Following a review of all events reported at the secondary level and not discussed elsewhere in the paper, no significant new safety information about the use of SEROQUEL in children was identified.

8. DISCUSSION

SEROQUEL is not approved for use in the pediatric population. The Children and Adolescents sub-section of Section 4.2 *Posology and Method of Administration* of the SEROQUEL Core Data Sheet (CDS) states the following:

> "The safety and efficacy of SEROQUEL have not been evaluated in children and adolescents."

A total of 65 reports (20 serious/45 non-serious) were identified from clinical trials with SEROQUEL, through 30 September 2004. No significant new safety issues were identified from a review of this data. Also, as of 30 September 2004, worldwide post-marketing reports received by AstraZeneca (AZ) comprised 840 reports for pediatric patients through 18 years of age. Of these, 724 were medically confirmed and 116 were not medically confirmed. Assessment of causality was difficult in these cases because of incomplete clinical information, unclear temporal sequence of exposure and outcome, confounding by concomitant medications for which the event or related events have been reported or by concurrent medical conditions, risk factors for the event, documented non-compliance, and/or alternative explanations. No significant new safety issues, including issues secondary to trans-placental or breast milk exposure, were identified from a review of the data. A review of the medical/scientific literature did not disclose any significant new safety issues for SEROQUEL.

It was estimated that about 335,000 pediatric patients have been exposed to SEROQUEL in the US for all time through 30 September 2004. No data was available for outside the US.

Following a review of all the available relevant clinical and safety information, as well as the medical/scientific literature, it was determined that the data do not identify any significant new safety issue regarding the use of SEROQUEL in pediatric patients. The safety profile for SEROQUEL in the pediatric population is similar to the known safety profile for SEROQUEL in the adult population.

AstraZeneca will continue to keep pediatric reports for SEROQUEL under careful review.

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