DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

MEMORANDUM

Office of Pediatric Therapeutics
Office of the Commissioner
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To: Robert Levin, M.D.
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Re: Addendum to OSE Safety Review of Seroquel® (quetiapine fumarate) and Seroquel ® XR (quetiapine fumarate extended-release); Examination of transplacental adverse event reports from the FDA Adverse Event Reporting System (FAERS) database (January 2010-July 2015) and from AstraZeneca's Global Patient Safety Database

Background

Seroquel® and Seroquel® XR (quetiapine fumarate and quetiapine fumarate extended-release) are commonly prescribed second generation antipsychotics (SGA) in the U.S., with an estimated 49 million prescriptions from outpatient retail pharmacies from August 2011-July 2015. There are no randomized, controlled studies of quetiapine in pregnant women, therefore post-marketing data are essential to the assessment of safety of quetiapine use during pregnancy. During the Pediatric Advisory Committee review process, it was noted that there were 155 FAERS reports related to intrauterine quetiapine exposure between August 1, 2011 and July 31, 2015. The FDA Office of Pediatric Therapeutics (OPT) reviewed these reports, plus an additional 65 reports received between January 1, 2010 and July 31, 2011.

The FAERS database has significant limitations, most prominently the reliance on voluntarily reported, non-standardized data of variable quality which frequently prevents causality assessment. Criteria that are commonly missing include duration of exposure, irresolvable issues such as polypharmacy, and in the case of intrauterine exposure, the period of pregnancy during which exposure occurred. Additionally, FAERS reports are inadequate for comparing the occurrence of common adverse outcomes in a general population to their occurrence in drug treated populations.

Summary of Adverse Event Reports

The purpose of this review was to evaluate whether there was any pattern of adverse events in prenatally-exposed live-born neonates that was not described in the current product labels for Seroquel® and Seroquel® XR. Section 8.1 of the product label contains the following:

"Pregnancy Category C:

Risk Summary: There are no adequate and well-controlled studies of SEROQUEL use in pregnant women. In limited published literature, there were no major malformations associated with quetiapine exposure during pregnancy. In animal studies, embryo-fetal toxicity occurred. Quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data: There are limited published data on the use of quetiapine for treatment of schizophrenia and other psychiatric disorders during pregnancy. In a prospective observational study, 21 women exposed to quetiapine and other psychoactive medications during pregnancy delivered infants with no major malformations. Among 42 other infants born to pregnant women who used quetiapine during pregnancy, there were no major malformations reported (one study of 36 women, 6 case reports). Due to the limited number of exposed pregnancies, these postmarketing data do not reliably estimate the frequency or absence of adverse outcomes. Neonates exposed to antipsychotic drugs (including SEROQUEL), during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization."

OPT completed the review of 220 adverse event reports submitted to FAERS between January 2010 and July 2015 associated with in utero exposure to Seroquel® and Seroquel® XR (Table 1). For the unlabeled adverse events, the number of events related to quetiapine as monotherapy is shown alongside the number of events that occurred in neonates born to women on polytherapy.

Table 1: Seroquel Transplacental Exposure FAERS Frequency (1/2010-7/2015)

	Number of Reports
TOTAL	**220**
Duplicates	27
Exclusions[§]	8
Fetal demise[†]	8
UNIQUE REPORTS OF LIVE BIRTHS	**177**
LABELED EVENTS	
Withdrawal syndrome (including irritability, insomnia)	67
Respiratory distress/Respiratory failure	66
Feeding problems	21
Abnormal tone (without other withdrawal symptoms)	12
Somnolence	6
UNLABELED EVENTS (# on monotherapy/ # on >1 medication)	
Premature birth (5*/22**)	27
Atrial septal defect (2*/7**)	9

Pyloric stenosis (3*/3**)	6
Talipes equinovarus (1*/5**)	6
Cleft lip and palate**	4
Ventricular septal defect (1*/3**)	4
Pulmonary stenosis or atresia (2*/2**)	4
Hypospadias*	3
Pierre-Robin sequence**	3
Brachydactyly *	2
Seizures **	2
Arachnoid cyst*	1
Cleft palate**	1
Ebstein's anomaly*	1
Esophageal atresia **	1
Esophageal atresia with tracheoesophageal fistula **	1
Shone's complex (aortic coarctation and valve stenosis)**	1
Supraventricular tachycardia and cardiomyopathy*	1
Teratoma**	1
Trisomy 18**	1
Trisomy 21**	1
Ventricular arrhythmia*	1

[§] Exclusions included 3 cases reported after the neonatal period, 1 report withdrawn, 1 exposure unrelated, 2 voluntary interruption of pregnancy, and 1 literature review submitted
[†] 3 were ≥ 34 weeks, 4 were < 34 weeks
[*] Women on quetiapine monotherapy
[**] Women on quetiapine plus at least 1 additional 1 psychoactive medication

Neonates with Trisomy 18 and 21 had associated congenital anomalies that were not listed in Table 1 as separate events. Congenital anomaly cases with more than one adverse event listed were:

- cleft palate, Pierre-Robin sequence, and prematurity
- pyloric stenosis and talipes equinovarus
- atrial septal defect and seizure
- pulmonary atresia, ventricular septal defect, and prematurity
- pulmonic stenosis and ventricular septal defect

Adverse event reports associated with the use of Seroquel® and Seroquel® XR from National Pregnancy Registry for Atypical Antipsychotics (NPRAA) and National Register of Antipsychotic Medication in Pregnancy (NRAMP) were requested from AstraZeneca, and reviewed. This review revealed 4 additional cases, including 1 neonate with anencephaly, 1 neonate with cleft lip and palate, 1 neonate with mitral valve regurgitation, cardiomegaly and persistent fetal circulation, and 1 neonate with transposition of the great vessels.

Discussion of registries and published literature

Registry data are another source of information used in safety assessment. In addition to the manufacturer's registry, additional registries have been established to provide outcome data from cohorts of women who were treated with antipsychotic medications during pregnancy. For example, National Register of Antipsychotic Medication in Pregnancy (NRAMP, Australia) was established in 2005 and has gathered a cohort of Australian women,[1]and the National Pregnancy Registry for Atypical Antipsychotics (NPRAA, U.S.) was established in Massachusetts in 2008.[2]

Regrettably, registry data may be limited by missing data elements and are confounded by referral bias and lack of generalizability. In the publications from SGA registries, it is notable that 43-69% of the pregnant women in the cohorts were on more than one psychoactive medication, which confounds assessment of causality.[1-3] Registry cohorts also have limited power to statistically demonstrate differences in adverse events. To show a doubling of the baseline rate of malformations of 1-3% with 80% power and an alpha error of 0.05, the sample size required would range from 1500-5000 exposed patients. Below are summarized the largest published samples involving prenatal exposure to quetiapine.

A systematic review of SGA exposure in pregnancy collected a total of 443 pregnancies exposed to quetiapine (from 9 studies plus the Swedish Birth Registry), with a combined rate of malformations of 3.6%.[4] The largest sample sizes in the systematic review were the Canadian and German cohorts, and it was notable in these publications that quetiapine was the most commonly used SGA in the cohort.[4] The Canadian cohort was self-referred to Motherisk, seeking evidence-based counseling about the effects of medication use during pregnancy.[5]

The German cohort was recruited prospectively through the Teratology Information Service. The cohort included 139 women who received quetiapine during pregnancy between 1997 and 2009. There were 5 malformations in the quetiapine group, for a rate of 3.59%. The authors concluded from their cohort of 561 women receiving SGAs that there was not an increased risk for significant malformations with SGA treatment during pregnancy.[3]

Two contemporary publications provide additional cohort data on pregnancies exposed to SGAs. NRAMP prospectively recruits women requiring antipsychotic medications during pregnancy or during the first 12 months after birth. A review of the first 147 pregnancies included 74 women who had received quetiapine (50% of the cohort). Two of their neonates were born with major malformations (2.7%)—one with cleft lip and palate and hydrocephalus and one with pulmonary atresia.[1] NPRAA reported on a cohort including 214 women with SGA exposure during the first trimester, and found a 1.4% rate of major malformations. All 3 neonates with malformations were born to women taking ≥2 psychoactive medications. This cohort has both notable strengths such as prospective enrollment and confirmation of outcomes as well as notable limitations, including a sample that was not necessarily representative of the patient population (in this cohort, the majority of participants were white, married, and college-educated).[2]

Conclusions

1) The phenomena of neonatal withdrawal syndrome, abnormal tone, feeding problems, and respiratory distress seen in neonates born to women who have taken Seroquel® or Seroquel®XR during the third trimester are described in the products' labels.

2) There does not appear to be an increased rate of significant congenital anomalies seen in neonates who have been exposed to Seroquel®/Seroquel®XR in-utero based on the available literature, though data from registries are underpowered for a definitive assessment.

3) Taking into consideration the limitations of the FAERS data, the review of this series of FAERS reports does not suggest a concerning pattern of congenital anomalies. Given the published data, the broad spectrum of anomalies noted in FAERS, and the

widespread use of Seroquel® and Seroquel®XR, it is unlikely that the FAERS reports suggest a new signal of clinical concern.

References:

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2. Cohen LS, Viguera AC, McInerney KA, et al. Reproductive Safety of Second-Generation Antipsychotics: Current Data From the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics. *Am J Psychiatry.* 2015:appiajp201515040506.
3. Habermann F, Fritzsche J, Fuhlbruck F, et al. Atypical antipsychotic drugs and pregnancy outcome: a prospective, cohort study. *J Clin Psychopharmacol.* 2013;33(4):453-462.
4. Ennis ZN, Damkier P. Pregnancy exposure to olanzapine, quetiapine, risperidone, aripiprazole and risk of congenital malformations. A systematic review. *Basic Clin Pharmacol Toxicol.* 2015;116(4):315-320.
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