APPLICATION NUMBER:

NDA 22-047 S-006, S-007, and S-008

OTHER REVIEW(S)
Maternal Health Team (MHT) Review

Date: July 25, 2008
Date Consulted: April 28, 2008

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To: Division of Psychiatry Products (DPP)

Drug: Seroquel XR (quetiapine fumarate) Extended Release Tablets

Subject: Seroquel labeling review

Materials Reviewed: Seroquel pregnancy and lactation published data.

Consult Question: As part of the DPP and MHT pilot labeling project, the MHT revised the Pregnancy and Nursing Mothers subsections of Seroquel labeling and included data from published studies. A formal review of the relevant published studies is provided in this consult.
EXECUTIVE SUMMARY

The Maternal Health Team (MHT) and the Safety Endpoints and Labeling Development (SEALD) Team have been working together to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 28, 2008). To further this effort, the MHT and DPP developed a pilot labeling project in which MHT selects labels to review from the DPP NDA/Supplemental NDA due date list. As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the pregnancy and nursing mothers label subsections.

On April 28, 2008, the MHT selected Supplemental NDA's 22-047/S-007 and 008 for Seroquel XR (quetiapine fumarate) Extended Release Tablets. Seroquel XR is an atypical antipsychotic currently approved for acute and maintenance treatment of schizophrenia. Supplement applications 007 and 008 propose two new indications, Bipolar Depression and Major Depressive Disorder (MDD). It is likely that Seroquel XR will be prescribed for women of child-bearing potential with bipolar depression or major depressive disorder.

Using a PubMed search, the following publications were found regarding the use of quetiapine during pregnancy or lactation:
- One prospective observational study of pregnant women treated with atypical antipsychotics. Placental transfer and obstetrical outcomes from drug exposure were reported.
- One placental transfer study of quetiapine using dually perfused placentas.
- One cohort study to determine pregnancy outcomes from atypical antipsychotic exposure.
- Six case reports of quetiapine exposure during pregnancy
- Seven case reports of quetiapine exposure during lactation

Based on quetiapine exposure in 63 women during pregnancy, no congenital malformations were reported. However, these data were based on two small studies and six case reports. In one study, nine infants born to mothers exposed to quetiapine experienced transient cardiovascular (two) or respiratory (seven) complications. However, the mothers were taking concomitant medications which included antiepileptics, SSRI/SNRIs, sedative hypnotics, and other psychotropics. Therefore, it is not clear whether these adverse events were related to quetiapine exposure.

There is also limited data on the effects of quetiapine use during lactation. Of eight women taking quetiapine and other drugs during lactation, no adverse effects were observed in the infants exposed to quetiapine through breast milk.

Schizophrenia and other mental illnesses are serious conditions that require treatment during pregnancy and lactation. While there is limited data available on exposure to quetiapine during pregnancy and breastfeeding, the data that is available is reassuring and should be included in the Pregnancy and Nursing Mothers sections of labeling.
Recommendations:
1. The Seroquel Pregnancy and Nursing Mothers subsections of labeling should be updated to include published human data. The MHT’s recommended revisions to the sponsors proposed labeling are provided on pages 21-23 of this review.

BACKGROUND

The Maternal Health Team (MHT) and the Safety Endpoints and Labeling Development (SEALD) Team have been working together to develop a more consistent and clinically useful structure for the Pregnancy and Nursing Mothers subsections of labeling that is in the spirit of the Proposed Pregnancy and Lactation Labeling Rule (published on May 28, 2008) while still complying with current regulations.

To further this effort, the MHT and DPP developed a pilot labeling project. As part of the pilot project, the MHT selects labels from the DPP NDA/Supplemental NDA due date list to review the Pregnancy and Nursing Mothers subsections of labeling. As part of the MHT labeling review, a literature search is conducted to determine if additional relevant published pregnancy and lactation data are available that would provide clinically useful information to healthcare professionals and their patients. If useful information is obtained from this search, the MHT includes that information in the Pregnancy and/or Nursing Mothers subsections of labeling.

On April 28, 2008, the MHT selected Supplemental NDA’s 22-047/S-007 and 008 for Seroquel XR (quetiapine fumarate) Extended Release Tablets. Seroquel XR is an atypical antipsychotic currently approved for acute and maintenance treatment of schizophrenia. Supplement applications 007 and 008 propose two new indications, Bipolar Depression and Major Depressive Disorder (MDD).

REVIEW OF DATA

This review provides a summary of published data on Seroquel use during pregnancy and lactation. Relevant pregnancy and lactation data from these studies will be recommended for inclusion in the Seroquel XR Pregnancy and Nursing Mothers subsections of labeling.

Pubmed search terms were:

- Pregnancy and quetiapine
- Pregnancy and Seroquel
- Fetus and Quetiapine
- Fetus and Seroquel
- Seroquel and lactation
- Quetiapine and lactation
- Quetiapine and neonate
- Quetiapine and breastfeeding
- Seroquel and lactation
- Seroquel and neonate
- Seroquel and breastfeeding


**Review of published data regarding Seroquel exposure during pregnancy:**
From a search of the literature using the search terms described above, the following publications were found:
- One prospective observational study of pregnant women treated with atypical antipsychotics. Placental transfer and obstetrical outcomes from drug exposure were reported.
- One placental transfer study of quetiapine using dually perfused placentas.
- One cohort study to determine pregnancy outcomes from atypical antipsychotic exposure.
- Six case reports of quetiapine exposure during pregnancy

A summary of these publications is provided below.

**Clinical studies (in order of most recent publication):**


   The aim of this study was to investigate the placental transfer of quetiapine using a dually perfused human placenta model and to assess the function of p-glycoprotein\(^1\) in the blood-placental barrier using two p-glycoprotein inhibitors (PSC833 and GG918).

   Eighteen term placentas (38 to 42 weeks gestation) were obtained after cesarean section (n=12) or normal vaginal delivery (n=6). Pregnancies were uncomplicated and mothers were healthy and took no medication during pregnancy.

   The authors found that quetiapine crossed the human placenta. The placental transfer of quetiapine was 3.7% which is 29% less than the transfer of freely diffusible anti-pyrene (reference agent). Therefore, the authors concluded that the blood-placental barrier partially limits the transfer of quetiapine across the placenta.

   *Reviewer comment: This was a placental transfer study. The study showed that quetiapine does cross the placental barrier.*


   Newport et.al conducted a prospective observational study of pregnant women treated with an atypical antipsychotic or haloperidol during pregnancy. Maternal and umbilical cord plasma samples were collected at delivery and analyzed for drug concentrations. Obstetrical outcomes were determined through maternal reports and obstetrical record reviews.

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\(^1\) The trophoblast layer of the placenta forms an anatomical functional barrier and includes several transporter proteins, including p-glycoprotein that decreases fetal exposure to drugs and environmental toxins.
Pregnant women who met the following inclusion criteria were recruited from Emory's Mental Health Program:

- \( \geq 18 \) years of age and able to provide informed consent
- receiving a stable daily dose of an antipsychotic for greater than five elimination half-lives at delivery
- allowed collection of maternal and umbilical cord plasma at delivery
- permitted laboratory confirmation of maternal compliance with the antipsychotic medication.

A total of 54 pregnant women were recruited and enrolled into the study (13 treated with haloperidol, 14 with olanzapine, 21 with quetiapine, and six with risperidone). The demographic, clinical characteristics and concomitant drug therapy of the women enrolled in the study are provided in Table 1 below.

**TABLE 1. Demographic and Clinical Characteristics of Pregnant Women**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Haloperidol (N=13)</th>
<th>Olanzapine (N=14)</th>
<th>Quetiapine (N=21)</th>
<th>Risperidone (N=6)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>F</td>
</tr>
<tr>
<td>Age (years)</td>
<td>30.5 (5.1)</td>
<td>30.8 (5.3)</td>
<td>31.7 (6.8)</td>
<td>27.7 (4.4)</td>
<td>0.76</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.2 (2.0)</td>
<td>14.7 (3.2)</td>
<td>14.1 (1.6)</td>
<td>12.0 (1.8)</td>
<td>1.99</td>
</tr>
<tr>
<td>Gravidity</td>
<td>2.5 (1.0)</td>
<td>2.7 (1.6)</td>
<td>3.2 (3.1)</td>
<td>3.0 (1.4)</td>
<td>0.40</td>
</tr>
<tr>
<td>Race</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Black/African American</td>
<td>3</td>
<td>23.1</td>
<td>4</td>
<td>28.6</td>
<td>3</td>
</tr>
<tr>
<td>American</td>
<td>1</td>
<td>7.7</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Native American</td>
<td>9</td>
<td>69.2</td>
<td>10</td>
<td>71.4</td>
<td>18</td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>2</td>
<td>15.4</td>
<td>3</td>
<td>21.4</td>
<td>8</td>
</tr>
<tr>
<td>Marital status</td>
<td>Never married</td>
<td>2</td>
<td>15.4</td>
<td>3</td>
<td>21.4</td>
</tr>
<tr>
<td>Married</td>
<td>10</td>
<td>76.9</td>
<td>11</td>
<td>78.6</td>
<td>12</td>
</tr>
<tr>
<td>Divorced</td>
<td>1</td>
<td>7.7</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Principal psychiatric</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td>diagnosis</td>
<td>Anxiety disorder</td>
<td>6</td>
<td>46.2</td>
<td>8</td>
<td>57.2</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>4</td>
<td>30.7</td>
<td>2</td>
<td>14.3</td>
<td>4</td>
</tr>
<tr>
<td>Depressive disorder</td>
<td>Psychotic disorder</td>
<td>3</td>
<td>23.1</td>
<td>4</td>
<td>28.8</td>
</tr>
<tr>
<td>Polytherapy at delivery</td>
<td>Any psychotropic</td>
<td>7</td>
<td>53.9</td>
<td>10</td>
<td>71.4</td>
</tr>
<tr>
<td>SSR/SNR\textsuperscript{a}</td>
<td>6</td>
<td>46.2</td>
<td>8</td>
<td>57.1</td>
<td>12</td>
</tr>
<tr>
<td>Sedative/hypnotic \textsuperscript{b}</td>
<td>2</td>
<td>15.4</td>
<td>3</td>
<td>21.4</td>
<td>6</td>
</tr>
<tr>
<td>Antiepileptic drug\textsuperscript{c}</td>
<td>1</td>
<td>7.7</td>
<td>1</td>
<td>7.1</td>
<td>8</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Agents used in polytherapy include citalopram (N=3), escitalopram (N=1), fluoxetine (N=6), fluvoxamine (N=1), paroxetine (N=3), sertraline (N=10), and venlafaxine (N=5).
\textsuperscript{b} Agents used in polytherapy include clonazepam (N=7), lorazepam (N=3), and zolpidem (N=2).
\textsuperscript{c} Drugs used in polytherapy include carbamazepine (N=1), lamotrigine (N=8), and topiramate (N=1).

Only 27.8% of the women enrolled in the study were receiving monotherapy prior to delivery. Concomitant medications included antidepressants, sedative-hypnotics, and antiepileptic drugs. A stratified analysis demonstrated that the quetiapine exposed group was more likely to be receiving poly-drug therapy, particularly with antiepileptic drugs (carbamazepine, lamotrigine, and topiramate).

Two of the 21 women exposed to quetiapine did not have maternal samples obtained to determine the placental passage ratio (ratio of umbilical cord plasma to maternal plasma).
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Of the remaining 19 women exposed to quetiapine, the mean placental passage ratio was 24.1% compared to 72.1% for olanzapine, 65.5% for haloperidol, and 49.2% for risperidone. The placental passage ratio for quetiapine was lower than all other antipsychotics included in the study.

Of all women enrolled in the study, there were:

- four preterm (<37 weeks estimated gestational age) deliveries (7.4%) [one in quetiapine group]
- six low birth weight (<2500 g) neonates (11.3%) [one in quetiapine group]
- three high birth weight (>4000 g) neonates (5.7%) [zero in quetiapine group]
- six neonatal intensive care unit admissions (11.3%)
  - seven with cardiovascular complications (13.2%) [two in quetiapine group]
  - 12 with respiratory complications (22.6%) [seven in quetiapine group]
  - two with hypotonia (3.8%) [zero in quetiapine group]

Table 2 below shows the placental passage ratios and obstetrical outcomes of women enrolled in the study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Haloperidol (N=13)</th>
<th>Olanzapine (N=14)</th>
<th>Quetiapine (N=21)</th>
<th>Risperidone (N=6)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placental passage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose at delivery (mg/day)</td>
<td>2.2 ± 1.7</td>
<td>8.9 ± 8.1</td>
<td>336.9 ± 272.3</td>
<td>3.0 ± 1.8</td>
<td></td>
</tr>
<tr>
<td>Continuous exposure before delivery (weeks)</td>
<td>22.0 ± 8.5</td>
<td>18.4 ± 14.2</td>
<td>28.9 ± 11.6</td>
<td>25.9 ± 14.1</td>
<td>F=2.38, df=3, p&lt;0.09</td>
</tr>
<tr>
<td>Cord plasma concentration (ng/ml)</td>
<td>1.15 ± 0.71</td>
<td>17.9 ± 16.2</td>
<td>7.8 ± 4.3</td>
<td>1.6 ± 1.0</td>
<td></td>
</tr>
<tr>
<td>Maternal plasma concentration (ng/ml)</td>
<td>4.53 ± 6.79</td>
<td>27.4 ± 20.8</td>
<td>35.8 ± 12.3</td>
<td>3.9 ± 2.9</td>
<td></td>
</tr>
<tr>
<td>Cord/maternal ratio (%)a</td>
<td>65.5 ± 40.3</td>
<td>72.1 ± 42.0</td>
<td>24.1 ± 11.2</td>
<td>33.9 ± 3.46</td>
<td>6.04, df=3, p&lt;0.002</td>
</tr>
<tr>
<td>Preterm delivery (≤37 weeks)</td>
<td>N = 3</td>
<td>N = 1</td>
<td>N = 1</td>
<td>N = 0</td>
<td>Fisher's Exact Test, df=3, p&lt;0.23</td>
</tr>
<tr>
<td>Obstetrical outcomesc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low birth weight (&lt;2500 g)</td>
<td>0 ± 0.0</td>
<td>4 ± 30.8</td>
<td>1 ± 4.8</td>
<td>1 ± 16.7</td>
<td>&lt;0.07</td>
</tr>
<tr>
<td>High birth weight (&gt;4000 g)</td>
<td>15.4 ± 1.9</td>
<td>7.6 ± 1.6</td>
<td>7.6 ± 1.0</td>
<td>9.7 ± 0.5</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>APGAR (1 minute)</td>
<td>7.4 ± 0.3</td>
<td>8.8 ± 0.4</td>
<td>8.9 ± 0.4</td>
<td>9.2 ± 0.4</td>
<td>1.22, df=3, p&lt;0.32</td>
</tr>
<tr>
<td>APGAR (5 minutes)</td>
<td>8.9 ± 0.3</td>
<td>8.8 ± 0.4</td>
<td>8.9 ± 0.4</td>
<td>9.2 ± 0.4</td>
<td>1.36, df=3, p&lt;0.27</td>
</tr>
<tr>
<td>Neonatal intensive care unit admission</td>
<td>N = 0 ± 0.0</td>
<td>N = 4 ± 30.8</td>
<td>N = 2 ± 9.5</td>
<td>N = 0 ± 0.0</td>
<td>&lt;0.09</td>
</tr>
<tr>
<td>Neonatal complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>2 ± 15.4</td>
<td>3 ± 23.1</td>
<td>2 ± 9.5</td>
<td>0 ± 0.0</td>
<td>&lt;0.61</td>
</tr>
<tr>
<td>Respiratory</td>
<td>1 ± 7.7</td>
<td>4 ± 30.8</td>
<td>7 ± 33.3</td>
<td>0 ± 0.0</td>
<td>&lt;0.16</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>1 ± 7.7</td>
<td>1 ± 7.7</td>
<td>0 ± 0.0</td>
<td>0 ± 0.0</td>
<td>&lt;0.46</td>
</tr>
</tbody>
</table>

a Four subjects were excluded from the cord/maternal ratio calculations owing to missing samples (haloperidol, N=1; olanzapine, N=1; quetiapine, N=2). Risperidone concentrations reported are the sum of the parent compound and the principal active metabolite.
bTukey's post hoc pairwise analysis demonstrated that quetiapine cord/maternal ratios were significantly lower than those for olanzapine (p<0.003) and haloperidol (p<0.02).
cOne subject (olanzapine, N=1) was excluded from all obstetrical outcome analyses other than preterm delivery owing to loss to follow-up.

A longer duration of antipsychotic therapy before delivery did not predict adverse obstetrical outcomes.
The authors concluded that all antipsychotics studied demonstrated incomplete placental passage and that quetiapine demonstrated the lowest placental passage of all the medications.

**Reviewer comment:**

- Women exposed to quetiapine had the lowest placental passage ratio compared to all other antipsychotics included in the study. This is consistent with the findings from Rahi et al., in which the placental passage of quetiapine was 29% less than the reference agent used in the study.

- Concomitant medications included antiepileptics, SSRI/ SNRIs, sedative hypnotics, and other psychotropics. Some infants born to mothers exposed to quetiapine experienced cardiovascular and respiratory complications. However, details on the severity, duration, and long term effects of these complications were not reported, and it is not possible to determine whether these adverse effects were due to quetiapine exposure, other drug exposures, or a combination of factors.

- On July 28, 2008 the author of this publication was emailed to determine severity, duration, and long term effects of complications observed in neonates exposed to quetiapine. Based on an email response from Dr. Newport on July 31, 2008, all complications observed in neonates exposed to quetiapine that did not require NICU admission were transient. Only two infants in the quetiapine group required NICU admission. One was admitted to the NICU (for 30 hours) after aspiration during delivery and was discharged home with mother and is doing well (now two years old). The other was admitted to NICU for two weeks for treatment of pneumonia. Dr. Newport’s email dated July 31, 2008 is provided in Appendix A of this review.


McKenna and colleagues conducted a cohort study to determine whether atypical antipsychotics increase the rate of major malformations above the 1% to 3% baseline risk seen in the general population.

The study enrolled pregnant women who contacted the Motherisk Program\(^2\) or the Israeli Teratogen Information Service\(^3\) and were taking an atypical antipsychotic during pregnancy. In addition, women taking an atypical antipsychotic within three months of pregnancy or during pregnancy were recruited from the Drug Safety Research Unit\(^4\)

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\(^2\) The Motherisk Program at The Hospital for Sick Children in Toronto, Ontario, Canada, is a counseling service that provides pregnant and breastfeeding women and health care providers with evidence-based information on the safety and risks of exposure to prescription and over-the-counter medications, natural health products, chemicals, radiation, and infectious agents.

\(^3\) The Israeli Teratogen Information Service is a service similar to Motherisk.

\(^4\) The Drug Safety Research Unit in Southampton, England, is an independent medical charity that conducts Prescription-Event Monitoring studies to monitor the safety of recently marketed medicines prescribed under the
database in England. All women were matched to a comparison group of pregnant women who were not exposed to these agents. Women who called the Motherisk program and the Israeli Teratogen Information Service were matched to a comparison group of women who called the Motherisk Program. Exposed women recruited from the Drug Safety Research Unit database were compared to other non-exposed women from the same database.

Exposed women identified from Motherisk and the Israeli Teratogen Information Service were contacted via telephone three to four months after their expected delivery date to assess pregnancy outcome. If consent was received, the teratogen information service also requested a report from the pediatrician treating the infant. Practitioners treating the women identified through the Drug Safety Research Unit were sent a questionnaire about the patient’s drug history and pregnancy outcome.

The pregnancy outcomes of 151 women exposed to an atypical antipsychotic during the first trimester were obtained [olanzapine (N = 60), risperidone (N = 49), quetiapine (N = 36), and clozapine (N = 6)]. Maternal characteristics were obtained for 105 women exposed to an atypical antipsychotic from Motherisk; however, the authors were unable to obtain this information for women recruited from the Israeli Teratogen Information Service or the Drug Safety Research Unit database.

Maternal characteristics of the Motherisk cohort are provided in Table 3 below.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Atypical Antipsychotic (N = 105)</th>
<th>Non-Teratogenic Agent (N = 105)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unplanned pregnancy</td>
<td>39 (57)</td>
<td>22 (33)</td>
<td>&lt;.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vitamin use</td>
<td>64 (85)</td>
<td>94 (98)</td>
<td>.005&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Yes</td>
<td>11 (15)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reported alcohol use</td>
<td>14 (14)</td>
<td>12 (12)</td>
<td>.834</td>
</tr>
<tr>
<td>Yes</td>
<td>87 (86)</td>
<td>89 (88)</td>
<td>.17</td>
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<tr>
<td>No</td>
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<tr>
<td>Level of alcohol consumption</td>
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<td></td>
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</tr>
<tr>
<td>Heavy/binge</td>
<td>5 (36)</td>
<td>1 (8)</td>
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<tr>
<td>Casual</td>
<td>9 (64)</td>
<td>11 (92)</td>
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<tr>
<td>Reported smoking</td>
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<td>&lt;.001&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Yes</td>
<td>38 (38)</td>
<td>13 (13)</td>
<td></td>
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<tr>
<td>No</td>
<td>63 (62)</td>
<td>88 (87)</td>
<td>.05&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ethnic background</td>
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</tr>
<tr>
<td>White</td>
<td>50 (76)</td>
<td>82 (83)</td>
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</tr>
<tr>
<td>Asian</td>
<td>7 (11)</td>
<td>11 (11)</td>
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<tr>
<td>Black</td>
<td>1 (2)</td>
<td>2 (2)</td>
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</tr>
<tr>
<td>Other</td>
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<tr>
<td>Living arrangements</td>
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<tr>
<td>With parents</td>
<td>2 (3)</td>
<td>3 (3)</td>
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</tr>
<tr>
<td>Single</td>
<td>11 (17)</td>
<td>5 (5)</td>
<td></td>
</tr>
<tr>
<td>Separated/divorced</td>
<td>2 (3)</td>
<td>1 (1)</td>
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</tr>
<tr>
<td>Married</td>
<td>51 (77)</td>
<td>92 (91)</td>
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</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td>&lt;.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Unemployed</td>
<td>22 (33)</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>Homemaker</td>
<td>22 (33)</td>
<td>20 (20)</td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>3 (5)</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>Work part-time</td>
<td>6 (9)</td>
<td>14 (14)</td>
<td></td>
</tr>
<tr>
<td>Work full-time</td>
<td>13 (20)</td>
<td>61 (60)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td>&lt;.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Public school</td>
<td>13 (20)</td>
<td>4 (4)</td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>18 (27)</td>
<td>20 (20)</td>
<td></td>
</tr>
<tr>
<td>College/university</td>
<td>3 (5)</td>
<td>5 (5)</td>
<td></td>
</tr>
<tr>
<td>Postgraduate</td>
<td>3 (5)</td>
<td>19 (19)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td>.99</td>
</tr>
<tr>
<td>Yes</td>
<td>6 (8)</td>
<td>6 (6)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>72 (92)</td>
<td>87 (94)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td>.30</td>
</tr>
<tr>
<td>Yes</td>
<td>1 (1)</td>
<td>5 (5)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>77 (99)</td>
<td>88 (95)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (pre-pregnancy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>kg/m²</td>
<td>58</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>27.80 (25%-75% quartile)</td>
<td>22.92 (20.52-27.37)</td>
<td>&lt;.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Minimum</td>
<td>16</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>45</td>
<td>39</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Values are shown as N (%). Total numbers of women vary among the characteristics due to missing data.

<sup>b</sup>Statistically significant.

Many women from the Motherisk cohort required poly-drug therapy during pregnancy. In addition to taking an atypical antipsychotic, 17 women (16%) also took a conventional antipsychotic, 60 (57%) took an antidepressant, and 18 (17%) took an anti-epileptic drug (13 used valproic acid, four used carbamazepine, three used lamotrigine, one used gabapentin, and one used topiramate).
Thirty-six women (34%) also took a benzodiazepine, of which the most commonly used was lorazepam (N=14). Other subjects used diazepam, clonazepam, temazepam, or alprazolam.

Six women (6%) used lithium at some point during their pregnancy, and five of the six women discontinued lithium after the pregnancy was confirmed.

**Reviewer comment:**
*No major malformations were reported in any of the babies exposed to anti-epileptics, benzodiazepines, or lithium.*

Significantly more women taking anti-psychotics chose to terminate their pregnancies, and there was a higher rate (not statistically significant) of spontaneous abortions in the exposed group (14.5% vs. 8.6%).

There was no statistical difference in the rates of reported complications during labor between the two groups, and there was no statistical difference in the rates of neonatal complications.

The rates of major malformations in the exposed and comparison groups were not statistically different [one (0.9%) in the exposed group versus two (1.5%) in the comparison group]. One baby, who was born to a woman using olanzapine, had multiple structural anomalies including cleft lip, encephalocele, and aqueductal stenosis. Table 4 below provides a comparison of pregnancy outcomes between exposed and control groups.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Comparison of Pregnancy Outcome Between Women Exposed to Atypical Antipsychotics and Non-Teratogenic Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td>Atypical Antipsychotic (N = 151)</td>
</tr>
<tr>
<td>Live birth, N</td>
<td>110 (1.4)</td>
</tr>
<tr>
<td>Spontaneous abortion, N (%)</td>
<td>22 (14.5)</td>
</tr>
<tr>
<td>Stillbirth, N (%)</td>
<td>4 (2.6)</td>
</tr>
<tr>
<td>Therapeutic abortion, N (%)</td>
<td>15 (9.9)</td>
</tr>
<tr>
<td>Major malformation, N (%)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Birth weight, mean (SD), g</td>
<td>3341 (685)</td>
</tr>
<tr>
<td>Gestational age at birth, mean (SD), wk</td>
<td>39 (1)</td>
</tr>
</tbody>
</table>

The authors concluded that atypical antipsychotics do not appear to increase the risk for major malformations.

**Reviewer comment:**
*There were no major malformations among babies born to pregnant women exposed to quetiapine, with or without other medications, during pregnancy.*
Case Reports (in order of most recent publication):


The authors describe the case of a 17-year-old pregnant adolescent who presented at the hospital for recurrent neurological symptoms due to pseudotumor cerebri, diagnosed two years prior to this admission. The patient had a past medical history of Bipolar II disorder and a sleep disorder. She had also been hospitalized for severe alcohol abuse.

Upon admission to the hospital, the patient’s psychiatric illness was evaluated; she was educated about the potential risks of psychotropic medication to the fetus; and she received counseling regarding medical abortion. Medical abortion was proposed by the neurologists because of the unforeseeable risks for both mother and fetus due to her neurological illness. In the past, the patient tried to stop her psychotropic medications; however, she relapsed immediately with either depression or hypomania and self-mutilation.

The patient decided to continue her pregnancy and current treatment for psychiatric illness, which included quetiapine 300 mg/day, venlafaxine ER 75 mg/day, and trazadone ER 150 mg/day. An ultrasound examination was performed at 13 and 20 weeks, and no fetal abnormalities were detected. Drug plasma level monitoring was performed four times during the first through third trimesters and at six months postpartum.

The patient’s mood was stable until four weeks before birth when she started to experience a depressed mood. Her medication was not increased due to the risk of neonatal withdrawal. However, her venlafaxine dose was increased to 150 mg immediately postpartum to treat depression and decreased four months postpartum to her pre-pregnancy dose.

The patient delivered a healthy baby boy (weight 3000 g, length 47 cm, Apgar scores 9/10/10). The baby experienced jitteriness during the first four days of life. At one year of age, the baby was normal and had met developmental milestones.

The patient’s quetiapine concentration levels and elimination remained unchanged during pregnancy; however, venlafaxine plasma levels were two-fold higher postpartum than during pregnancy despite equal dosing at the time of measurement. In addition, there were no changes in plasma levels or elimination rates between the first, second, and third trimesters of pregnancy.

Reviewer comment: The authors state that venlafaxine plasma levels were two-fold higher postpartum than during pregnancy despite equal dosing at the time of measurement. However, they also state that the patient’s venlafaxine dose was increased to 150 mg immediately postpartum to treat depression. Therefore, the venlafaxine
plasma measurement may have been taken just prior to the increase in dose; however, this is not stated by the authors.

Area under the concentration versus time curve (AUC) was calculated for the observed sampling intervals. The authors found that the AUC values were lower during pregnancy for quetiapine and venlafaxine (no data available for trazodone). Therefore, the authors concluded that quetiapine and venlafaxine bioavailability is much lower during pregnancy than postpartum.

Reviewer comment:
The infant's gestational age at delivery was not provided. The adolescent mother was exposed to quetiapine, venlafaxine, and trazodone during pregnancy. No congenital malformations were reported. However, the authors found a decrease in quetiapine and venlafaxine bioavailability during pregnancy.


This is a case report of a 30 year old woman hospitalized during her 21st week of pregnancy for bipolar affective disorder complicated by a manic episode and psychotic features. At this time, she was started on quetiapine 400 mg/day titrated to 1200 mg/day at the end of two weeks. After three weeks of treatment, haloperidol 15mg/day was added to treat psychomotor agitation. The patient was closely monitored throughout pregnancy. No obstetrical complications occurred. All ultrasound measurements were normal.

Quetiapine was continued throughout pregnancy but was tapered over nine weeks and stopped just before delivery.

At 39 weeks gestation, a male infant was delivered via cesarean section. The infant weighed 3400g, was 48cm in length, and had Apgar scores of 8 and 10.

The infant was followed until 80 days of life and had normal neurological and psychomotor development.

Reviewer comment:
The patient used haloperidol and quetiapine during pregnancy and delivered a healthy baby with normal neurological and psychomotor development.


Gentile described a 33 year old Caucasian woman exposed to quetiapine and fluvoxamine during her second pregnancy. The mother was previously diagnosed with severe postpartum psychotic depression following the birth of her first child. She had since been successfully treated with quetiapine 400mg and fluvoxamine 200mg daily. These
medications were continued throughout her second pregnancy along with folic acid supplementation. Her pregnancy was normal, and no fetal abnormalities were observed during ultrasound examinations. Due to an intrauterine myoma, delivery was by scheduled cesarean section. Gestational age at time of delivery was not reported. The healthy baby girl weighed 2600g and had Apgar scores 9 and 10.

The mother breastfed the baby; however, due to decreased milk production, formula supplementation was required. Mixed feeding continued for three months and no adverse effects were observed in the infant. At the time of the report, the baby continued to show normal developmental milestones.

Reviewer comment:
Healthy baby born to mother exposed to quetiapine and fluvoxamine during pregnancy. The mother breastfed and formula fed the baby without any reported adverse effects. At the time of the report, the baby achieved normal developmental milestones.


The authors describe a case report of a 36 year old, multigravida, Caucasian woman with schizophrenia exposed to multiple drugs during pregnancy to control her psychiatric disorder and agitations.

The patient was not aware of her pregnancy until she was hospitalized. Pregnancy was diagnosed at 22 weeks gestation and no congenital malformations were observed during an ultrasound examination.

After diagnosis of pregnancy, the patient’s quetiapine dose was decreased to 500 mg/day (previous dose was 600 mg/day, eight to 21st weeks gestation); carbamazepine, fluvoxamine, alprazolam and biperiden were stopped. Table five below lists all drugs the patient was exposed to during pregnancy including the gestational time at exposure:

Table 5

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/day)</th>
<th>Gestation week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirtazapine</td>
<td>30</td>
<td>1–5</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>300</td>
<td>1–5</td>
</tr>
<tr>
<td>Diazepam</td>
<td>10</td>
<td>4–5</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>12.5</td>
<td>4–7</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>150</td>
<td>6–7</td>
</tr>
<tr>
<td>Risperidone</td>
<td>4</td>
<td>6–7</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>100</td>
<td>8–21</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0.5</td>
<td>8–21</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>600</td>
<td>8–21</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>22–37</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>600</td>
<td>8–21</td>
</tr>
<tr>
<td>Biperiden</td>
<td>2</td>
<td>8–21</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>10</td>
<td>31–36</td>
</tr>
<tr>
<td>Ampicillin + sulbactam</td>
<td>1500</td>
<td>31–32</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>40</td>
<td>31–32</td>
</tr>
<tr>
<td>Oxcarbinate</td>
<td>1500</td>
<td>31–37</td>
</tr>
</tbody>
</table>
The patient was again hospitalized in the 31st week because of thrombophlebitis. She was treated with ampicillin/subactam, oxerutine and enoxaparin.

A healthy, normal female infant was vaginally delivered at 37 weeks gestation. The infant weighed 3000 g, was 50 cm in length, and had Apgar scores of 8 and 9. No developmental abnormalities were observed at four months of age.

Reviewer comment: 
Mother exposed to multiple drugs throughout pregnancy including quetiapine. The baby was healthy baby with no developmental abnormalities at four months of age.


The authors describe a case report of a 33 year-old woman who experienced her first episode of psychosis during pregnancy. The patient was initially treated with risperidone 4mg/day. After two weeks, she was switched to quetiapine 300mg/day because of high prolactin levels and poor clinical response.

Pregnancy was diagnosed at four weeks gestation, and after two weeks of quetiapine treatment. Quetiapine was continued throughout pregnancy. Her initial maintenance dose of 300 mg/day was reduced to 200 mg/day at week 21. Four weeks before the patient's estimated due date, quetiapine dose was decreased by 50 mg/day each week to enable breastfeeding after birth.

At 39 weeks gestation, the patient delivered a healthy baby girl with Apgars 8 and 9 and weight 3610g. No problems developed in the first month postpartum. There was no exacerbation of psychosis, and successful breast-feeding was initiated.

Reviewer comment: Case report of a woman exposed to quetiapine and risperidone during pregnancy. Healthy baby delivered.


The authors describe a case report of a 38 year-old woman, with a history of schizophrenia (paranoid type) treated with quetiapine during pregnancy.

The patient was initially treated with zuclopenthixol and then changed to quetiapine 300 mg/day. Pregnancy was diagnosed at 17 weeks gestation. The patient was taking quetiapine since conception. At 20 weeks gestation, the patient’s dose of quetiapine was decreased to 200 mg twice a day. By 22 weeks gestation, the patient was taking 150 mg twice a day due to symptom improvement.

---

5 European drug that acts on the complex of varicose symptoms.
6 Zuclopenthixol is used in the United Kingdom to treat psychotic disorders.
At 38 weeks gestation, the patient delivered a healthy baby boy with Apgar scores of 9 and 10 and weight .3120 g. The infant’s development was normal during the first six months of life.

Reviewer comment:
Case report of a woman exposed to quetiapine during pregnancy. Healthy baby was delivered with normal development at six months of life.

Review of published case reports on Seroquel exposure during lactation (in order of most recent publication):


The authors describe a case report of a 26 year old woman prescribed quetiapine 400mg for treatment of depression complicated with chronic pain.

The patient initially received quetiapine 300mg. The dose was increased to 400mg during her fourth month of pregnancy. Concurrent medications throughout her pregnancy included oxycodone 20 mg three times daily and fluoxetine 40 mg daily. The patient delivered a male baby weighing 3.4kg at 37 weeks gestation.

The transfer of quetiapine into breast milk was assessed when the infant was three months old and weighed 5.6 kg. The baby was considered opiate-dependent at birth and was receiving oral morphine 120 μg, three times daily at the time of the milk study. He was otherwise healthy. Venous blood samples were collected immediately before the mother's quetiapine dose and at 12.8 and 23.1 hours after the dose. Sixteen milk samples were collected by manual expression at regular feeding times over a 24 hour period starting immediately before the quetiapine dose and at 0.75 hours and 4.75 hours after the maternal dose.

The plasma and milk concentration time data for quetiapine are shown in Figure 1 below.

**Figure 1.**

[Graph showing concentration-time data for quetiapine]
The average concentration of quetiapine in milk was 41 μg/L. The absolute infant dose was 6.2 μg/kg/day based on an estimated infant milk intake of 0.15 L/kg/day. The relative infant dose was 0.09% of the weight-adjusted maternal dose. The infant's plasma quetiapine level was 1.4 μg/L, which is equivalent to 6% of the maternal plasma concentration. The M:P ratio calculated from samples in the elimination phase was 0.29. The infant did not experience any adverse effects during breastfeeding. The authors did note that clearance of quetiapine in the infant was lower than that in the mother.

Reviewer comment:
*Infant was exposed to quetiapine, morphine, and fluoxetine during breastfeeding. Infant was on morphine taper for opiate dependence in the postpartum period. No adverse effects were observed in the infant. The relative infant dose was 0.09% of the weight-adjusted maternal dose.*


The authors examined the secretion of quetiapine in combination with venlafaxine, trazodone, paroxetine, and/or clonazepam in breast milk and developmental assessments of the exposed babies.

Six participants were recruited from a larger study of perinatal psychotropic medication use. The women were receiving quetiapine in combination with either a selective serotonin reuptake inhibitor or a selective norepinephrine reuptake inhibitor. One participant was also taking clonazepam.

Expressed breast milk samples were taken at variable times after dosing. Ingestion estimates were based on infant breast milk ingestion of 0.15 L/kg per day for babies younger than 3 months, and 0.10 L/kg per day for babies three to six months. The babies' motor, mental, and behavioral development was assessed using the Bayley Scales of Infant Development, Second Edition (BSID-II).

Reviewer comment:
The authors did not provide the times that breast milk samples were collected.

Table 6 below lists the maternal psychiatric diagnosis, medications taken, breast milk levels, and estimated infant exposure of the women enrolled in the study.
Table 6
Maternal Psychiatric Diagnoses, Breast Milk Medication Levels, and Estimated Infant Exposure

<table>
<thead>
<tr>
<th>Participant</th>
<th>Maternal Psychiatric Diagnosis</th>
<th>Medications</th>
<th>Quetiapine Added</th>
<th>Maternal Dose, mg</th>
<th>Breast Milk Sample Taken</th>
<th>Medication Level in Breast Milk, nmol/L</th>
<th>Estimated Volume of Milk Ingested, L/kg Per Day</th>
<th>Total Daily Exposure to Baby, mg/kg Per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>MDD</td>
<td>Quetiapine</td>
<td>16.5 wk postpartum</td>
<td>25</td>
<td>ND*</td>
<td>0.10</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OCD</td>
<td>Paroxetine (IR)</td>
<td>60</td>
<td>ND</td>
<td>ND</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clonazepam</td>
<td></td>
<td>0.5</td>
<td>ND</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>MDD</td>
<td>Quetiapine</td>
<td>3 wk postpartum</td>
<td>25</td>
<td>ND</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OCD</td>
<td>Paroxetine (CR)</td>
<td>12.5</td>
<td>ND</td>
<td>ND</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>MDD</td>
<td>Quetiapine</td>
<td>18-wk gestation</td>
<td>50</td>
<td>ND</td>
<td>0.10</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>Paroxetine (IR)</td>
<td>40</td>
<td>ND</td>
<td>ND</td>
<td>0.10</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>MDD</td>
<td>Quetiapine</td>
<td>Before conception</td>
<td>75</td>
<td>ND</td>
<td>0.15</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>Trazodone</td>
<td></td>
<td>75</td>
<td>108</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Venlafaxine</td>
<td></td>
<td>75</td>
<td>371</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>MDD</td>
<td>Quetiapine</td>
<td>10.5 wk postpartum</td>
<td>400</td>
<td>ND</td>
<td>0.10</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OCD</td>
<td>Paroxetine (IR)</td>
<td>50</td>
<td>ND</td>
<td>264</td>
<td>&lt;0.10</td>
<td>&lt;0.10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Venlafaxine</td>
<td></td>
<td>776</td>
<td>0.10</td>
<td>&lt;0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>MDD</td>
<td>Quetiapine</td>
<td>35.5-wk gestation</td>
<td>100</td>
<td>32</td>
<td>0.15</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BPD</td>
<td>Venlafaxine</td>
<td></td>
<td>225</td>
<td>1179</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>with dissociation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ND indicates not detected (<30 nmol/L).

In four of the six cases (A, B, C, and D), quetiapine was not detected in the breast milk. In the remaining cases (E and F) estimated levels of quetiapine exposure were less than 0.01 mg/kg per day (F) and 0.10 mg/kg per day (E).

In case B, BSID-II scores were in the slightly delayed range on the Mental and Motor Scales, but were within normal limits on the Behavioral Scale. In case C, BSID-II scores were within one point of the normal range on the Mental Development Index and within normal range on all other scales.

Babies B and C were exposed to low levels of quetiapine and paroxetine with minimal estimated exposure to both medications. Therefore, the authors state that a direct association between medication exposure during breastfeeding and developmental effects cannot be inferred from this sample.

The authors concluded that infants were exposed to low levels of medication through breastmilk. In addition, no association between developmental outcomes and exposure to multiple drugs was observed.

Reviewer comment:
Breastfeeding mothers were exposed to quetiapine and other antidepressants. Only two of the six women had detectable levels of quetiapine in breast milk. Estimated infant exposure was less than 0.01 mg/kg per day and 0.10 mg/kg per day. The authors did not attribute any developmental effects to quetiapine exposure through breast milk. In addition, no adverse effects in the nursing infants were reported.

The authors describe a case report of a 39 year old woman taking quetiapine during breastfeeding to treat Bipolar Disorder Type I (mixed mood state, moderate severity) with post-partum onset.

The patient had a past medical history of major depressive episodes. She was treated for worsening depression with paroxetine 20mg at four months postpartum. At six months postpartum, she started quetiapine 200mg twice daily.

The patient breastfed regularly while taking quetiapine and paroxetine. No adverse effects were observed in the nursing infant. No additional details were provided by the authors.

**Reviewer comment:**
*Case report of a breastfeeding woman taking quetiapine and paroxetine at six months postpartum. No adverse effects were observed in the nursing infant.*


The authors describe a case report of a 36 year old woman who took quetiapine 200 mg/day throughout her pregnancy and wished to continue treatment while breastfeeding.

Since no published literature existed at the time of the case report, the patient decided to formula feed her infant until breast milk measurements of quetiapine could be obtained.

At three weeks postpartum, manually expressed breastmilk samples were collected over a six hour period. Samples were obtained before quetiapine dosing and again at one, two, four, and six hours after dosing.

The daily amount of quetiapine ingested by a nursing infant was calculated by assuming an infant ingests 150 ml/kg/day of breastmilk and by using the average milk concentration of quetiapine over six hours. The maximum amount ingested by an infant was calculated based on the highest milk concentration.

The average milk concentration of quetiapine over six hours was 13 µg/L, with a maximum concentration of 62 µg/L at one hour. Levels of quetiapine rapidly fell to almost pre-dosing levels by two hours. The authors estimated that an exclusively breastfed infant would ingest 0.09% of the weight-adjusted maternal dose. The maximum amount an infant would ingest based on the highest milk concentration was 0.43% of the weight-adjusted maternal dose.
After reviewing the results of the milk study, the patient began exclusively breastfeeding her infant at eight weeks postpartum. At four and a half months of age, the infant was developing well and no adverse effects from breastfeeding were reported.

The authors concluded that the level of infant exposure to quetiapine in breastmilk appears to be small and not significant enough to produce pharmacological effects.

Reviewer comment:
This is a case report of the quetiapine breastmilk levels in one woman. The average milk concentration of quetiapine over six hours was 13 µg/L, with a maximum concentration of 62 µg/L at one hour. The authors estimated that an exclusively breastfed infant would ingest 0.09% of the weight-adjusted maternal dose. The maximum amount an infant would ingest based on the highest milk concentration was 0.43% of the weight-adjusted maternal dose.

In addition to the reports described above, the National Library of Medicine's, Drugs and Lactation Database describes three additional case reports.


A nursing mother was taking quetiapine 200 mg daily. Quetiapine was undetectable (<5 mcg/L) in breast milk.


One mother took oral quetiapine 25 mg daily during pregnancy and continued to take quetiapine 50 mg daily during lactation. At six weeks of age, the infant was doing well. No further follow-up was reported.


A nursing mother with postpartum psychosis was started on quetiapine 25 mg daily at six weeks postpartum along with unspecified benzodiazepines. The quetiapine dosage was increased gradually to 200 mg daily over the next six weeks and up to 300 mg daily over the next four weeks (16 weeks postpartum). The mother was also started on mirtazapine 15 mg daily at eight weeks postpartum.

Breastfeeding was stopped at 16 weeks postpartum because of reduced milk production. During breastfeeding, the infant was excessively drowsy until the benzodiazepine dosage was decreased. At the same time as the benzodiazepine dosage adjustment, her quetiapine dosage was increased. The infant was followed for at least two months after breastfeeding
stopped. No effects on the infant’s growth, motor or psychological development or signs of infant withdrawal were noted.

Sponsors Proposed Labeling

**Highlights - Use in Specific Populations**

**DISCUSSION AND CONCLUSIONS**

Many women of childbearing age suffer from schizophrenia and other mental illnesses that require use of antipsychotics, such as Seroquel, during pregnancy and lactation.
Based on quetiapine exposure in 63 women during pregnancy, no congenital malformations were reported. However, this data was based on two small studies and six case reports. In one study, infants born to mothers exposed to quetiapine experienced transient cardiovascular and respiratory complications. In addition, the mothers were taking concomitant medications which included antiepileptics, SSRI/SNRIs, sedative hypnotics, and other psychotropics. Therefore, it is not known whether these adverse events were due to quetiapine exposure.

There is also limited data on the effects of quetiapine use during lactation. Of eight women taking quetiapine and other drugs during lactation, no adverse effects were observed in the infants exposed to quetiapine through breast milk.

Schizophrenia and other mental illnesses are serious conditions that require treatment during pregnancy and lactation. While there is limited data available on exposure to quetiapine during pregnancy and breastfeeding, the data that is available is reassuring and should be included in the Pregnancy and Nursing Mothers sections of labeling.

**Recommendations:**

1. The MHT recommends the following revisions be made to the Seroquel Pregnancy and Nursing Mothers subsections of labeling based on review of published reports provided on pages 3-20 of this review. Recommended additions are underlined and deletions are struck out.

**Highlights**

Use in Specific Populations

- **Pregnancy:** Limited human data. Based on animal data, may cause fetal harm (8.1).
- **Nursing Mothers:** Caution should be exercised when administered to a nursing woman (8.3).

8.2 **Pregnancy**

Pregnancy Category C:

There are no adequate and well-controlled studies of SEROQUEL XR use in pregnant women. In limited published literature, there were no congenital 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.

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 developmental anomalies. However, in the quetiapine exposed group, nine infant’s had transient cardiovascular (2) or respiratory (7) complications at birth. 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).

When pregnant rats and rabbits were exposed to quetiapine during organogenesis, there was evidence of developmental toxicity in the offspring. There were no major structural malformations, but delays in skeletal ossification occurred in rats at 0.6 and 2.4 times and maximum recommended human dose (MRHD) and in rabbits at 1.2 and 2.4 times the MRHD on a mg/m² basis. At 2.4 times the MRHD, there was an increased incidence of carpal/tarsal flexure (minor soft tissue anomaly) in rabbit offspring and decreased fetal weights in both species. Maternal toxicity (decreased body weights and/or death) occurred at 2.4 times the MRHD in both species [see Nonclinical Toxicology (13.3)].

In a peri/postnatal reproductive study in rats, no drug-related effects were observed when pregnant dams were treated with quetiapine at doses 0.01, 0.12, and 0.24 times MRHD (on a mg/m² basis). However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 3.0 times the MRHD (on a mg/m² basis).

8.3 Nursing Mothers
SEROQUEL XR is excreted into human milk. Caution should be exercised when SEROQUEL XR is administered to a nursing woman.
In published case reports, the average concentration of quetiapine in breast milk ranged from undetectable to 62 μg/L. Infant quetiapine levels from breast milk ranged from undetectable to 1.4 μg/L. The estimated infant dose ranged from 0.09% to 0.43% of the weight-adjusted maternal dose. No adverse events have been reported in infants exposed to quetiapine through breast milk.

13.3 Reproductive and Developmental Toxicity

The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 mg/kg or 0.3 to 2.4 times the maximum human dose on a mg/m$^2$ basis or in rabbits at 25 to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m$^2$ basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m$^2$ basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m$^2$ basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m$^2$ basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m$^2$ basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study.

In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m$^2$ basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m$^2$ basis.
Appendix A: Email response dated July 31, 2008 from Dr. Newport

From: Jeff Newport [dnewpor@emory.edu]
Sent: Thursday, July 31, 2008 5:50 AM
To: Araojo, Richardae
Subject: RE: Atypical Antipsychotic and Pregnancy Publication

Thanks for your interest. Complications reported for the neonates (exposed to any of the 4 antipsychotics) who did not require NICU admission were transitional at delivery.

In the quetiapine group, only 2 infants required NICU admission. One was admitted to the NICU for 30 hours after aspiration during delivery – was discharged home with mother and has done well since (now 2 years old). The other was admitted to NICU for 2 weeks for treatment of pneumonia.

Four of the olanzapine infants required NICU admission. One was admitted for a brief overnight NICU stay for supplemental oxygen and a “septic screen”. The second was in the NICU for 2 weeks due to fever of unknown origin – treated empirically for infection though source was never identified. The third was admitted to the NICU for 3.5 months due to complications related to a cardiac septal defect and esophageal atresia. Incidentally, infant #3 was NOT exposed to olanzapine during first trimester (ie organogenesis). The fourth infant was admitted to NICU due to supraventricular tachycardia and “minimal respiratory effort.” Infant #4 received CPAP and Narcan to reverse effects of fentanyl administered during delivery. This child was also reported to have a patent ductus arteriosus. This mother/infant dyad was lost to follow-up – therefore, the duration of NICU stay and subsequent infant outcome is unknown.

None of the risperidone or haloperidol infants required NICU admission.

I hope this proves helpful.

Jeff

THE INFORMATION TRANSMITTED IN THIS ELECTRONIC COMMUNICATION IS INTENDED ONLY FOR THE PERSON OR ENTITY TO WHOM IT IS ADDRESSED AND MAY CONTAIN CONFIDENTIAL AND/OR PRIVILEGED MATERIAL. ANY REVIEW, RETRANSMISSION, DISSEMINATION OR OTHER USE OF OR TAKING OF ANY ACTION IN RELIANCE UPON, THIS INFORMATION BY PERSONS OR ENTITIES OTHER THAN THE INTENDED RECIPIENT IS PROHIBITED. IF YOU RECEIVED THIS INFORMATION IN ERROR, PLEASE CONTACT THE SENDER AND THE PRIVACY OFFICER, AND PROPERLY DISPOSE OF THIS INFORMATION.

From: Araojo, Richardae [mailto:richardae.araojo@fda.hhs.gov]
Sent: Monday, July 28, 2008 12:49 PM
To: jeff.newport@emory.edu
Subject: Atypical Antipsychotic and Pregnancy Publication

Dear Dr. Newport,

I am a clinical pharmacist and reviewer with the Maternal Health Team at FDA. We are working on adding published data to certain drug labels and found your article published in 2007 entitled, “Atypical Antipsychotic Administration During Late Pregnancy: Placental Passage and Obstetrical Outcomes”.

We found your publication very helpful and we have one question regarding neonatal outcomes. In the quetiapine exposed group, cardiovascular complications occurred in 2 neonates and 7 experienced
respiratory complications. Were these complications transitional at birth or did they persist. If they persisted, how long did they take to resolve. Also, were there any prolonged hospitalizations among these neonates.

Any information you can provide would be most helpful.

Many thanks,
Chardae

*****************************************************************************
Richardae Taylor Arajo, Pharm.D., LCDR USPHS
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff
FDA/CDER/OND, Immediate Office
Ph: (301) 796-1152
Fax: (301) 796-9858
Email: richardae.arajo@fda.hhs.gov

---------------------------------------------------------------------
Richardae Arajo, Pharm.D.
Regulatory Reviewer, Maternal Health Team

---------------------------------------------------------------------
Karen Feibus, MD
Team Leader, Maternal Health Team

---------------------------------------------------------------------
Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
Chardae Araojo
7/31/2008 01:17:31 PM
CSO

Karen Feibus
7/31/2008 02:16:52 PM
MEDICAL OFFICER
Signing for CDR Lisa Mathis, MD
DSI CONSULT: Request for Clinical Inspections

Date: February 6, 2008

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46
Joe Salewski., Branch Chief (Acting), GCP2, HFD-47
Name of DSI Primary Reviewer (if known)

Through: Thomas P. Laughren, M.D., Director
Division of Psychiatry Products / HFD-130

From: Doris J. Bates, Ph.D, Senior Regulatory Health Project Manager
Division of Psychiatry Products / HFD-130

Subject: Request for Clinical Site Inspections

I. General Information

Application#: NDA-22-047:
SE1-006 [bipolar depression],
SE1-007 [bipolar mania monotherapy]

Sponsor: AstraZeneca
Sponsor contact information: See Attachment 1 for details
Drug: Seroquel XR (quetiapine fumarate) Extended Release Tablets
NME: Yes/No
Standard or Priority: Standard or Priority
Study Population < 18 years of age: Yes/No
Pediatric exclusivity: Yes/No

PDUFA:
Action Goal Date: October 19, 2008
Inspection Summary Goal Date: July 19, 2008

II. Background Information

Include a brief introduction about the application and include the following:

• New application or supplement? Reason for supplement
  Efficacy Supplement. For additional details, please see Attachment 1.
• Proposed indication
  Please see above.
• Brief information
  o on drug
  o disease
NDA 22-047 S-006, S-007
Request for Clinical Inspections

- pivotal studies (to include brief summary of protocols, pertinent endpoints, and concerns with application)

Please see Attachment 2.

III. Protocol/Site Identification

Include the Protocol Title/# for all protocols to be audited. Complete the following table.

<table>
<thead>
<tr>
<th>NDA # and S #</th>
<th>Indication</th>
<th>Site Information</th>
<th>Protocol #</th>
<th>Number of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA 22-047 S-006</td>
<td>Treatment of Bipolar Depression</td>
<td>Vikram Mehran R D Clinical Research, Inc.</td>
<td>D144CC00002.</td>
<td>20 enrolled / 12 randomized</td>
</tr>
<tr>
<td>NDA 22-047 S-007</td>
<td>Treatment of Bipolar Mania, acute, monotherapy</td>
<td>10101 Southwest Freeway Suite 340 Houston, TX 77074 [for CV see Attachment 3]</td>
<td>D144CC00004</td>
<td>33 enrolled / 12 randomized</td>
</tr>
</tbody>
</table>

**Protocol Titles:**

D144CC00002
A Multicenter, Double-blind, Randomized, Parallel-group, Placebocontrolled, Phase III Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL®) Sustained-release as Monotherapy in Adult Patients with Acute Bipolar Depression

D144CC00004
A Multicenter, Double-blind, Randomized, Parallel-group, Placebocontrolled, Phase III Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL®) Sustained-release as Monotherapy in Adult Patients with Acute Bipolar Mania

IV. Site Selection/Rationale

An audit is necessary to assure that studies upon which we are basing a possible marketing approval were conducted under GCP. The site chosen for audit has enrolled a reasonable number of patients, is within the continental US, and participated in the pivotal studies for both of the supplements for which an audit has been requested.

**Domestic Inspections:**

Reasons for inspections (please check all that apply): See above.
NDA 22-047 S-006, S-007
Request for Clinical Inspections

Should you require any additional information, please contact Doris J. Bates, Ph.D., at 301-796-1040, or Cara Alfaro, Pharm.D., at 301-796-1033.

Concurrence: (as needed)

____________________ Medical Team Leader
____________________ Medical Reviewer
____________________ Director, Division Director (for foreign inspection requests only)

Attachments:
- Attachment 1: Cover letters for S-006 and S-007
- Attachment 2: Synopsis from Pivotal Trial Study Reports for S-006 and S-007.
- Attachment 3: CV for Dr. Mehra
Attachment 1
AstraZeneca

18 December 2007

Thomas P. Laughren, MD
Division Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Ammendale Road
Beltlsville, MD 20705-1266

RE: NDA 22-047
SEROQUEL® XR (quetiapine fumarate) Extended Release Tablets
Supplemental New Drug Application – Bipolar Depression

Dear Dr. Laughren:

In accordance with Section 505(b) of the Federal Food, Drug and Cosmetic Act and Section 314 of Title 21 of the Code of Federal Regulations (21 CFR 314), AstraZeneca Pharmaceuticals LP (AstraZeneca) hereby submits this supplemental New Drug Application (sNDA 22-047) for the indication of SEROQUEL® XR (quetiapine fumarate) Extended Release Tablets as treatment for bipolar depression. This submission is made on behalf of AstraZeneca UK Limited. A letter authorizing AstraZeneca to serve as the US agent is included.

This sNDA includes the results of a single pivotal efficacy study, Study D144CC00002. On November 6, 2006, in response to AstraZeneca’s End of Phase II briefing document the Division indicated that a single positive study in bipolar depression with SEROQUEL® XR would be sufficient to obtain approval for a bipolar depression claim.

**Submission Structure**
This supplement is being provided in eCTD format. It contains all the required Module 1 components. As agreed with the Division in correspondence dated 15 October 2007, no Clinical Summaries have been provided in Module 2 since this supplement contains the findings of a single clinical trial. Module 2 contains an introduction, and a Non-Clinical Overview and Non-clinical Summary to support revisions to the labeling regarding mechanism of action. Module 4 contains the supporting non-clinical studies to Module 2. Module 5 contains the Clinical Study Report for Study D144CC00002, as well as the required case report tabulations, patient profiles and case report forms. There is no new Chemistry, Manufacturing and Controls information with this supplement and therefore Module 3 is cross-referenced to NDA 22-047. All other non clinical information is cross-referenced to NDA 20-639.

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355
Please note that a literature review for quetiapine, covering 1 August 2006 through 31 July 2007, was provided in the PSUR filed on 27 September 2007.

Study D144CC00002 utilized good clinical practices (GCP) in compliance with the Institutional Review Board (IRB) requirements in 21 CFR 56, and informed consent requirements in 21 CFR 50. This study was performed entirely in the United States under IND 76,176.

**Pediatric Studies**
This supplement includes a request for waiver for investigations of SEROQUEL XR in children under 10 years of age and a deferral for investigations in adolescents aged 10-17 years of age in Module 1.

**Risk Management Plan**
(b)(4)

**Field Copy**
In accordance with 21 CFR 314.50(d)(1)(v), AstraZeneca certifies that a field copy of this sNDA is not applicable, as no new CMC information is included.

**Financial Disclosure**
As required in 21 CFR 54.4, a certification (Form 3454) is enclosed regarding the financial interests and arrangements for all of the clinical investigators who contributed to the clinical study submitted in this application. In addition, a certification statement is enclosed which states that AstraZeneca did not and will not use, in any capacity, the services of any person debarred under section 306(a) or (b).

**PDUFA Payment**
Further, as required in Section 736(a)(1)(A)(i) of the Prescription Drug User Fee Act (PDUFA), AstraZeneca UK Limited, with AstraZeneca as the US agent, provided payment in the amount of $589,000.00 on 10 December 2007. This amount represents full payment of the application fee. The User Fee ID Number for sNDA 22-047 is [b](4).

**Administrative Information**
Attached to this cover letter, for the convenience of the Division is the list of key FDA Interactions for this supplement.
This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.5.5001 (Corporate Edition), with a virus definition file dated 13-December 2007. No viruses were detected, and AstraZeneca certifies that the submission is virus-free.

This submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to exemption 4 of the Freedom of Information Act and FDA regulations, and the disclosure of which is prohibited by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and other applicable law. Pursuant to FDA regulations, AstraZeneca is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event that FDA determines that all or any part of this submission may be disclosed.

Please do not hesitate to contact me, or in my absence, Patricia Patterson, Associate Director, at (302) 885-1539.

Sincerely,

Gerald Limp, Director
Regulatory Affairs
Telephone: (302) 886-8017
Fax: (302) 886-2822

GL/MCM

Desk Copy: Thomas Laughren, MD; Room No.4114, Silver Spring, MD
Doris Bates, PhD; Room No. 4102, Silver Spring, MD
18 December 2007

Thomas P. Laughren, MD
Division Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 22-047
SEROQUEL® XR (quetiapine fumarate) Extended Release Tablets
Supplemental New Drug Application – Bipolar Depression

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1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355
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**Risk Management Plan**

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Sincerely,

Gerald Limp, Director
Regulatory Affairs
Telephone: (302) 886-8017
Fax: (302) 886-2822

GL/MCM

Desk Copy: Thomas Laughren, MD; Room No.4114, Silver Spring, MD
Doris Bates, PhD; Room No. 4102, Silver Spring, MD
18 December 2007

Thomas P. Laughren, MD
Division Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 22-047
SEROQUEL® XR (quetiapine fumarate) Extended Release Tablets
Supplemental New Drug Application – Acute Bipolar Mania

Dear Dr. Laughren:

In accordance with Section 505(b) of the Federal Food, Drug and Cosmetic Act and Section 314 of Title 21 of the Code of Federal Regulations (21 CFR 314), AstraZeneca Pharmaceuticals LP (AstraZeneca) hereby submits this supplemental New Drug Application (sNDA 22-047) for the indication of SEROQUEL® XR (quetiapine fumarate) Extended Release Tablets as treatment for acute bipolar mania. This submission is made on behalf of AstraZeneca UK Limited. A letter authorizing AstraZeneca to serve as the US agent is included.

This sNDA includes the results of a single pivotal efficacy study, Study D144CC00004. On November 6, 2006, in response to AstraZeneca’s End of Phase II briefing document the Division indicated that a single positive study in acute bipolar mania with SEROQUEL® XR would be sufficient to obtain approval for a claim in acute bipolar mania. AstraZeneca understands that the intent of the FDA was not to require a full duplication of all clinical studies/all dosing options between the two quetiapine presentations, but to establish that SEROQUEL XR tablets can effectively treat bipolar illness. Therefore, AstraZeneca is seeking approval for the treatment of acute bipolar mania, both as monotherapy and as adjunct to mood stabilizers.

Submission Structure
This supplement is being provided in eCTD format. It contains all the required Module 1 components. As agreed with the Division in correspondence dated 15 October 2007, no Clinical Summaries have been provided in Module 2 since this supplement contains the findings of a single clinical trial. Module 2 contains an introduction, only. Module 5 contains the Clinical Study Report for Study D144CC00004, as well as the required case report.
tabulations, patient profiles and case report forms. No new non clinical data is provided in this supplement and therefore, cross reference is made to NDA 20-639 and NDA 22-047, sequence 0008 for bipolar depression. There is no new Chemistry, Manufacturing and Controls information with this supplement and therefore, Module 3 is cross-referenced to NDA 22-047.

Please note that a literature review for quetiapine, covering 1 August 2006 through 31 July 2007, was provided in the PSUR filed on 27 September 2007.

The SEROQUEL® XR clinical study utilized good clinical practices (GCP) in compliance with the Institutional Review Board (IRB) requirements in 21 CFR 56, and informed consent requirements in 21 CFR 50. The clinical study for this submission was performed entirely in the United States under IND 76,176.

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This supplement includes in Module 1, a request for a waiver for investigations of SEROQUEL® XR in children under 10 years of age and a deferral for investigations in adolescents aged 10-17 years of age.

**Risk Management Plan**

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Administrative Information
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Please do not hesitate to contact me, or in my absence, Patricia Patterson, Associate Director, at (302) 885-1539.

Sincerely,

Gerald Limp, Director
Regulatory Affairs
Telephone: (302) 886-8017
Fax: (302) 886-2822

GL/MCM

Desk Copy: Thomas Laughren, MD; Room No.4114, Silver Spring, MD
Doris Bates, PhD; Room 4102, Silver Spring, MD
A Multicenter, Double-blind, Randomized, Parallel-group, Placebo-controlled, Phase III Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL®) Sustained-Release as Monotherapy in Adult Patients With Acute Bipolar Depression

International co-ordinating investigator
Trisha Suppes, MD, PhD

Study center(s)
This study was conducted at 64 study centers in the United States (US). Sixty-one (61) sites completed procedures and received drug; 3 sites did not enroll patients.

Publications
There were no publications based on this study by the date of final approval.

Study dates
First patient enrolled 01 December 2006
Last patient completed 21 June 2007

Phase of development
Therapeutic confirmatory (III)

Objectives
The primary objective of this study was to evaluate whether quetiapine fumarate extended-release (XR)\(^1\) formulation at a dose of 300 mg once daily (QD) demonstrated superior efficacy compared to placebo in patients with bipolar depression, after 8 weeks of treatment.

---

\(^1\) Referred to as quetiapine sustained-release (SR) in the protocol.
Secondary objectives were:

- To evaluate whether quetiapine XR is effective in decreasing depressive symptoms in both patients with rapid and non-rapid cycling
- To evaluate whether quetiapine XR is superior to placebo in achieving remission in bipolar depression
- To evaluate whether quetiapine XR is superior to placebo in achieving response in bipolar depression
- To evaluate the efficacy of quetiapine XR compared to placebo in the treatment of a broad range of symptoms of bipolar depression
- To evaluate the safety and tolerability of quetiapine XR QD in patients with bipolar depression.

**Study design**

This was an 8-week multicenter, double-blind, randomized, parallel-group, placebo-controlled, Phase III study of the efficacy and safety of quetiapine XR 300 mg QD given in the evening as monotherapy in the treatment of patients with an acute depressive episode in the framework of bipolar I or II disorder. This study consisted of an up to 35-day enrollment period followed by an 8-week treatment period with 1 of 2 treatment regimens (quetiapine XR 300 mg or placebo). Quetiapine XR was not down-titrated at the end of the study.

**Target patient population and sample size**

The per protocol plan was to enroll approximately 400 patients, with approximately 280 randomized to receive study treatment to obtain 266 evaluable patients (i.e., patients receiving at least 1 dose of investigational product that had at least 1 post-baseline MADRS assessment).

Patients were male or female outpatients (not hospitalized), 18 to 65 years of age, inclusive, with a diagnosis of bipolar I or bipolar II disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Text Revision 4th Edition (DSM IV TR) criteria most recent episode depressed (296.50-296.54 and 296.89 respectively) confirmed by the amended version of the Structured Clinical Interview for DSM-IV-TR. Patients who experienced rapid cycling course, defined as ≥4 episodes of mood disturbance but ≤8 episodes in the previous 12 months (mood episode defined as depressed, manic, mixed, or hypomanic) were allowed to participate.

To be enrolled in the study, patients must have had a Hamilton Rating Scale for Depression (HAM-D, 17-item) total score of ≥20, a HAM-D Item 1 (depressed mood) score ≥2 at enrollment (Visit 1) and randomization (Visit 2) and have had a Young Mania Rating Scale (YMRS) ≤12 at enrollment (Visit 1) and randomization (Visit 2).
In order to meet the statistical requirements of the study, it was estimated that a total of approximately 400 patients were required for enrollment. It was also anticipated that 280 patients would be randomized, resulting in 266 evaluable patients.

**Investigational product and comparator(s): dosage, mode of administration and batch numbers**

Quetiapine XR or placebo matching quetiapine XR tablets 50 mg, 200 mg, and 300 mg were orally administered QD, in the evening.

**Duration of treatment**

Eligible patients had a washout and enrollment period of up to 35 days. Following the washout and enrollment period, patients entered an 8-week treatment period. Patients were required to be outpatient (not hospitalized) at randomization.

**Criteria for evaluation (main variables)**

**Efficacy**

**Efficacy**

**Primary outcome variable:**

- Change from baseline (randomization [Visit 2]) in depression symptoms by final visit (Visit 10) as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) total score

**Secondary variables supporting the primary objective**

- MADRS Total Score response (patients with ≥50% reduction) from baseline (randomization [Visit 2]) to final visit (Visit 10)
- MADRS total score remission (patients with a MADRS total score ≤12 at final visit [Visit 10] assessment)
- Change from baseline (randomization [Visit 2]) to final visit (Visit 10) assessment in the Clinical Global Impression - Bipolar - Severity of Illness (CGI-BP-S)
- Final visit (Visit 10) assessment of Clinical Global Impression - Bipolar - Change (CGI-BP-C)
- Proportion of patients at final visit (Visit 10) with a CGI-BP-C of “Much improved” or “Very much” improved
- Change from baseline (randomization [Visit 2]) to final visit (Visit 10) in MADRS item scores.
Secondary outcome variables:

- Change from baseline (randomization [Visit 2]) in depressive symptoms in rapid and non-rapid cyclers to final visit (Visit 10) as measured by the MADRS total score
- Percentage decrease in MADRS total score at final visit (Visit 10)
- Improvement in clinical Global Impression-Bipolar (CGI-BP) from baseline (randomization [Visit 2]) to final visit (Visit 10)

Safety variables

- Proportion of patients with serious adverse events (SAEs) in the different treatment groups.
- AEs that led to withdrawal; proportion of patients withdrawing due to AE.
- Incidence of AEs and the change from baseline in laboratory values, vital signs, weight and the proportion of patients with a ≥7% increase in weight from baseline to final visit
- EPS (including akathisia) as measured by the change in Simpson Angus Scale (SAS) score and Barnes Akathisia Rating Scale (BARS) score to final visit and AEs of EPS, physical examinations and ECG
- Proportion of patients with treatment-emergent mania (AE of mania or hypomania defined as YMRS score ≥16 on 2 consecutive assessments or final assessment)
- Incidences of suicidality using a suicidality classification similar to the one established by Columbia University in the 2 treatment groups

Statistical methods

The power was set at 90% for a 2-sided test at α=0.05 for the comparison between quetiapine 300 mg XR formulation to placebo, using a 4 unit difference from placebo with a pooled standard deviation of 10.

Efficacy analyses were based on the following patient populations, defined prior to unblinding of the data:

The modified intention to treat (MITT) analysis set (Full analysis set) included all randomized patients who received ≥1 dose of study treatment and who had baseline (randomization [Visit 2]) values and at least one post-randomization MADRS assessment, classified by the randomized treatment assignment. Data from the MITT analysis set were used for analysis of the efficacy objectives.
The Intent-to-treat (ITT) analysis set included all randomized patients who took ≥1 dose of study medication, classified according to the randomized treatment assignment. Data from the ITT analysis set was used for sensitivity analysis of the primary variable.

The per-protocol (PP) analysis set, a subset of the MITT analysis set, included patients who had no major protocol violations or deviations effecting efficacy. Data from this population were used for a consistency check only for the analysis of the primary objective.

The safety analysis set included all randomized patients who took at least one dose of study medication, classified according to the treatment actually received.

**Patient population**

A total of 418 patients who were screened to achieve the planned sample size of 280 randomized patients, there were 138 screen failures. The most common reason for screen failure was incorrect enrolment, defined as the patient did not meet the required inclusion/exclusion criteria (25.4%); 3.6% patients were lost-to-follow-up.

Two hundred eighty patients were randomized, 140 in each treatment group. Similar percentages of randomized patients completed the study in each treatment group; 62.1% in the quetiapine XR group, and 68.6% in the placebo group.

The majority of patients in each treatment group completed the study. Among all randomized patients, the most common reason for discontinuation from the study was an AE, reported for a higher percentage of patients in the quetiapine XR group (12.1%) than placebo (1.4%). A higher percentage of patients in the quetiapine XR group (8.6%) compared to placebo (5.7%) were lost-to-follow-up. A higher percentage of patients in the placebo group were discontinued from the study due to lack of therapeutic response (7.1%) than quetiapine XR (1.4%).

At least 98% of patients in each group were classified as being compliant on the basis of tablet counts that were consistent with ≥70% consumption of doses.

Baseline demographic and weight characteristics are shown in Table S1.

---

2 Reasons for discontinuation are from the discontinuation page of the case report form.
<table>
<thead>
<tr>
<th>Demographic or Baseline Characteristic</th>
<th>Quetiapine XR (n=133)</th>
<th>Placebo (n=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45 (33.8%)</td>
<td>51 (37.2%)</td>
</tr>
<tr>
<td>Female</td>
<td>88 (66.2%)</td>
<td>86 (62.8%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>39.0 (11.3)</td>
<td>39.9 (12.8)</td>
</tr>
<tr>
<td>Median</td>
<td>39</td>
<td>40</td>
</tr>
<tr>
<td>Min, Max</td>
<td>18, 64</td>
<td>18, 64</td>
</tr>
<tr>
<td>Age category (years) n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 - 39</td>
<td>69 (51.9%)</td>
<td>67 (48.9%)</td>
</tr>
<tr>
<td>40 - 65</td>
<td>64 (48.1%)</td>
<td>70 (51.1%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>96 (72.2%)</td>
<td>98 (71.5%)</td>
</tr>
<tr>
<td>Black/ African American</td>
<td>29 (21.8%)</td>
<td>31 (22.6%)</td>
</tr>
<tr>
<td>American Indian/ Alaskan Native</td>
<td>3 (2.3%)</td>
<td>3 (2.2%)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (1.5%)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Native Hawaiian/ Pacific Islander</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (2.3%)</td>
<td>3 (2.2%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>88.7 (22.1)</td>
<td>88.9 (22.7)</td>
</tr>
<tr>
<td>Median</td>
<td>86.4</td>
<td>86.4</td>
</tr>
<tr>
<td>Min, max</td>
<td>48, 142</td>
<td>49, 158</td>
</tr>
<tr>
<td>BMI (kg/cm²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>31.6 (7.9)</td>
<td>30.8 (7.1)</td>
</tr>
<tr>
<td>Median</td>
<td>30.0</td>
<td>29.9</td>
</tr>
<tr>
<td>Min, max</td>
<td>18, 55</td>
<td>17, 50</td>
</tr>
<tr>
<td>BMI (kg/cm²) category, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to &lt;18.5</td>
<td>1 (0.8%)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>18.5 to &lt;25</td>
<td>23 (17.3%)</td>
<td>30 (21.9%)</td>
</tr>
<tr>
<td>25 to &lt;30</td>
<td>42 (31.6%)</td>
<td>38 (27.7%)</td>
</tr>
<tr>
<td>30 to &lt;40</td>
<td>47 (35.3%)</td>
<td>54 (39.4%)</td>
</tr>
<tr>
<td>≥40</td>
<td>20 (15.0%)</td>
<td>14 (10.2%)</td>
</tr>
</tbody>
</table>

BMI Body mass index. MITT Modified Intention to Treat. SD Standard deviation.
The 2 treatment groups were well matched with respect to demographic and baseline characteristics. A higher percentage of patients in both groups were female; 66.2% and 62.8% for quetiapine XR and placebo, respectively. Mean age was 39 to 40 years. The majority of patients were Caucasian; 72.2% and 71.5% for quetiapine XR and placebo, respectively, followed by Black/African American (21.8% and 22.6% for quetiapine XR and placebo, respectively).

In the MITT population, the 2 treatment groups were well-matched with respect to baseline weight parameters. Mean weight and BMI were 88.7 kg and 31.6 kg/cm² for quetiapine XR and 88.9 kg and 30.8 kg/cm² for placebo. By BMI category, there were slightly more patients in the 30 to <40 kg/cm² category for placebo (39.4%) than quetiapine XR (35.3%). The ≥40 kg/cm² category had slightly more quetiapine XR patients (15.0%) than placebo (10.2%).

Baseline disease characteristics are shown in Table S2.

### Table S2  Baseline disease characteristics and psychiatric history (MITT population)

<table>
<thead>
<tr>
<th></th>
<th>Quetiapine XR</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline disease characteristics, MITT population</td>
<td>n = 133</td>
<td>n = 137</td>
</tr>
<tr>
<td>Baseline MADRS total score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>29.8 ± 5.2</td>
<td>30.1 ± 5.5</td>
</tr>
<tr>
<td>Min, max</td>
<td>14 to 47</td>
<td>15 to 47</td>
</tr>
<tr>
<td>Baseline CGI-S depression score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>4.5 ± 0.6</td>
<td>4.5 ± 0.6</td>
</tr>
<tr>
<td>Min, max</td>
<td>3 to 7</td>
<td>3 to 6</td>
</tr>
<tr>
<td>Baseline CGI-S mania score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.6 ± 0.7</td>
<td>1.5 ± 0.7</td>
</tr>
<tr>
<td>Min, max</td>
<td>1 to 3</td>
<td>1 to 3</td>
</tr>
<tr>
<td>Baseline CGI score, overall bipolar illness score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>4.5 ± 0.6</td>
<td>4.4 ± 0.7</td>
</tr>
<tr>
<td>Min, max</td>
<td>3 to 6</td>
<td>1 to 6</td>
</tr>
<tr>
<td>Psychiatric history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSM-IV-TR diagnosis n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar I disorder</td>
<td>107 (80.5)</td>
<td>110 (80.3)</td>
</tr>
<tr>
<td>Bipolar II disorder</td>
<td>26 (19.5)</td>
<td>27 (19.5)</td>
</tr>
<tr>
<td>Rapid cycling n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>97 (72.9)</td>
<td>99 (72.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>36 (27.1)</td>
<td>38 (27.7)</td>
</tr>
</tbody>
</table>
Table S2  Baseline disease characteristics and psychiatric history (MITT population)

<table>
<thead>
<tr>
<th></th>
<th>Quetiapine XR</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years since bipolar diagnosis</td>
<td>n=132</td>
<td>n=137</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>18.8 (11.3)</td>
<td>19.7 (11.3)</td>
</tr>
<tr>
<td>Median</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Min, max</td>
<td>2 to 47</td>
<td>2 to 50</td>
</tr>
<tr>
<td>Duration of present depressive episode (weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>19.3 (12.8)</td>
<td>18.1 (11.2)</td>
</tr>
<tr>
<td>Median</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Min, max</td>
<td>0.6 to 57.6</td>
<td>4.3 to 52.1</td>
</tr>
<tr>
<td>Attempted suicide n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>91 (68.4)</td>
<td>87 (63.5)</td>
</tr>
<tr>
<td>Yes</td>
<td>42 (31.6)</td>
<td>50 (36.5)</td>
</tr>
</tbody>
</table>

CGI Clinical Global Impression; CGI-S Clinical Global Impression Severity; DSM-IV Diagnostic and Statistical Manual of Mental disorders, 4th edition; MADRS Montgomery-Asberg Depression Rating Scale; MITT Modified-intention-to-treat; SD Standard deviation.

Overall, study patients had moderate to severe depression as shown by validated scales of depression. Mean baseline MADRS and HAM-D scores were approximately 30 and 25, respectively (HAM-D scores not shown in table). Mean baseline CGI-BP overall severity scores for bipolar illness were similar; 4.5 for the quetiapine group and 4.4 for the placebo group. Mean baseline CGI-BP severity score for depression was 4.5 for both groups. In both groups, approximately 80% had bipolar 1 diagnosis and approximately 27% in each group had rapid cycling.

Per protocol, lorazepam up to 2 mg/day for severe anxiety was permitted in the study. Lorazepam use was consistent and similar from week to week in both treatment groups. From Week 1 through Week 8, lorazepam was taken by approximately 9% to 10% of quetiapine XR patients, and 10% to 11% of placebo patients, by number of patients in the study by week. From Week 1 to Week 8 of the randomized treatment period, sleep medication use was consistent and was taken by a higher percentage of placebo patients (14% to 16%) than quetiapine XR patients (9% to 10%), by number of patients in the study by week. From Week 1 to Week 8 of the randomized treatment period, anticholinergics were taken by approximately 5% to 7% of quetiapine XR and 5% to 6% of placebo patients in the study by week.

Efficacy results
Key efficacy results are presented for the MITT population in Table S3.
Table S3.  Key efficacy results (LOCF, MITT population)

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Quetiapine XR (n=133)</th>
<th>Placebo (n=137)</th>
<th>p-value at Week 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 1</td>
<td>Week 8</td>
<td>Week 1</td>
</tr>
<tr>
<td>MADRS change, LS mean, n (SE)</td>
<td>-10.16 (0.91)</td>
<td>-17.43 (1.24)</td>
<td>-6.54 (0.87)</td>
</tr>
<tr>
<td>Proportion with ≥50% MADRS response, n (%)</td>
<td>35 (26.5%)</td>
<td>87 (65.4%)</td>
<td>23 (16.9%)</td>
</tr>
<tr>
<td>Proportion with MADRS remission (total score &lt;12), n (%)</td>
<td>26 (19.7%)</td>
<td>72 (54.1%)</td>
<td>14 (10.3%)</td>
</tr>
<tr>
<td>CGI-BP-S overall LS mean change from baseline (SE)</td>
<td>-</td>
<td>-1.82</td>
<td>-</td>
</tr>
<tr>
<td>CGI-BP-C overall, LS mean change from baseline (SE)</td>
<td>3.03 (0.10)</td>
<td>2.38 (0.13)</td>
<td>3.47 (0.09)</td>
</tr>
<tr>
<td>CGI-BP-C much improved or very much improved, n (%)</td>
<td>37 (28.0%)</td>
<td>84 (63.2%)</td>
<td>22 (16.2%)</td>
</tr>
</tbody>
</table>

CGI-BP-S Clinical Global Impression Bipolar Severity scale; CGI-C Clinical Global Impression Change; LOCF Last observation carried forward; LS Least square; MITT Modified-Intention-to-Treat; MADRS Montgomery-Asberg Depression Rating Scale; SE Standard error. XR Extended release.

In patients with bipolar disorder, quetiapine XR at a dose of 300 mg QD was demonstrated to be superior to placebo in reducing the level of depressive symptoms as early as Day 8 (Week 1) and for up to 8 weeks of treatment, as assessed by the change from baseline in the total MADRS score (p<.001). At the end of the 8-week course of treatment, quetiapine XR patients in the MITT population had a least square (LS) mean decrease -5.5 points (standard error 1.2) greater than placebo-treated patients (P<.001). Quetiapine XR patients were 2.5x (relative risk=2.50) more likely to achieve MADRS response (≥50% reduction) at end-of-treatment than placebo patients. Quetiapine XR patients were 1.8x more likely to achieve remission (total score ≤12) as placebo patients (relative risk=1.81).

In addition, both bipolar I and II patients and rapid and non-rapid cycling patients treated with quetiapine XR 300 mg QD showed statistically significant greater improvements in MADRS total score compared to patients treated with placebo. For bipolar I patients least squares (LS) mean versus placebo was -6.5 (95% confidence interval [CI] -9.05, -4.00; p<.001) and for bipolar II patients LS mean versus placebo was -4.4 (95% CI -7.91, -0.80; p=.016). For patients with rapid cycling, LS versus placebo was -6.8 (95% CI -11.92, -1.76; p=.008) and for patients with non-rapid cycling LS versus placebo was -5.7 (95% CI -7.98, -3.51; p<.001).
Analysis of other secondary outcome variables also supported the superiority of quetiapine XR over placebo in the treatment of depression in patients with bipolar disorder. For most secondary outcome variables the treatment advantage for quetiapine XR was apparent by Day 8 (Week 1) and continued through Day 57 (Week 8). The proportion of patients showing ≥50% reduction in MADRS total score (responders) was statistically significantly higher for the quetiapine XR group compared to the placebo group by Week 2 and continued to end-of-treatment (p<.001). Likewise, the proportion of patients showing a MADRS total score ≤12 (remitters) was statistically significantly higher for the quetiapine XR group compared to the placebo group by Week 1 and continued to end-of-treatment (p<.05). Change in CGI Severity of Illness score was also statistically significant at Week 8 (p<.001). Quetiapine XR, at a dose of 300 mg QD, significantly improved a broad range of symptoms, including core symptoms of depression, as assessed by the item analysis of the MADRS. Item scores for suicidal thoughts and lassitude were improved numerically with quetiapine XR but were not statistically significant.

Safety results

A summary of AEs is presented in Table S4.

Table S4  Overview of adverse events during randomized treatment period (safety population)

<table>
<thead>
<tr>
<th>AE category</th>
<th>Number of patients(^a) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quetiapine XR (N=137)</td>
</tr>
<tr>
<td>Any AE</td>
<td>121 (88.3%)</td>
</tr>
<tr>
<td>Any AE with an outcome of death</td>
<td>0</td>
</tr>
<tr>
<td>Any SAE</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Any SAE leading to discontinuation of treatment</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Any AE leading to discontinuation of treatment</td>
<td>18 (13.1%)</td>
</tr>
<tr>
<td>Any other significant AE(^b)</td>
<td>0</td>
</tr>
</tbody>
</table>

AE  Adverse event; N number of patients; SAE  Serious adverse event. XR Extended release.
\(^a\)  Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
\(^b\)  Any AE that led to dose of treatment temporarily stopped, or deemed by the sponsor to be significant, excluding AEs reported as SAEs or led to discontinuation of treatment.

Note: Events were reported as AEs if they occurred after first dose to 30 days post-randomization.

The 300 mg QD dose of quetiapine XR was generally well tolerated. The percentage of patients with AEs was higher in the quetiapine XR (88.3%) versus the placebo group (68.6%). There were no deaths in the study; there were 2 SAEs in each group. The SAEs were asthma and depression in the quetiapine XR group; both patients with SAEs in the placebo group had suicidal ideation. The percentage of patients with discontinuation of treatment due to any AE
was higher in the quetiapine XR (13.1%) than placebo group (3.6%).³ Most AEs were mild or moderate in intensity and the majority resolved by the end of study. Events of the nervous and gastrointestinal systems were most common. Two of the most common AEs, somnolence and sedation, tended to occur within the first week of treatment. A higher percentage of quetiapine XR patients (77.4%) had AEs considered by the investigator to be related to study drug, compared to placebo (40.7%).

The incidences of AEs potentially related to EPS were low in each treatment group; 4.4% for quetiapine XR and 0.7% for placebo with the majority reported as mild to moderate. In the quetiapine XR group, 4 patients had AEs of EPS that resolved while on treatment. There were no AEs of neutropenia, agranulocytosis, or QTc prolongation. One AE of diabetes mellitus occurred prior to randomization to quetiapine XR. An AE related to suicidality (suicidal ideation) was reported for 1 patient (0.7%) in the quetiapine XR group and 2 placebo patients (1.4%). One “other significant AE of hypotension” was reported for 1 placebo patient (0.7%) and no quetiapine XR patient.

For lipids, percentages of patients with shifts from normal to clinically-important high total cholesterol values were higher for quetiapine XR than placebo; 6 (7.1%) and 3 (2.8%) of patients, respectively. Percentages of patients with shifts from normal at baseline to clinically-important high triglycerides at end of treatment were similar for quetiapine XR (8.3%) and placebo (7.5%). Percentages of patients with shifts from normal at baseline to clinically-important low HDL-C at end of treatment were similar for quetiapine XR (9.0%) and placebo (7.2%). Percentages of patients with shifts from normal at baseline to clinically-important high LDL-C at end-of-treatment were 3.5% for quetiapine XR and 1.9% for placebo.

Mean changes in glucose regulation laboratory parameters were generally higher for quetiapine XR patients with diabetic risk factors; there was no trend for patients without diabetic risk. Among non-diabetic patients, a higher percentage of placebo patients (12; 21.8%) than quetiapine XR patients (6; 12.0%) had glucose ≥100 and <126 mg/dL at Week 8. The percentages of patients with glucose or HbA1c outside of the specified ranges at Week 8 was otherwise similar for quetiapine XR and placebo overall by diabetic risk category.

Including triglycerides, among patients with <3 metabolic risk factors at baseline, 17.0% (17/100) in the quetiapine XR group and 10.1% (9/89)⁴ in the placebo group had ≥3 treatment-emergent metabolic risk factors.

Treatment-emergent criterion for increase in waist circumference was met by a higher percentage of quetiapine XR patients (9.9%) than placebo (6.6%). Shifts for other subcriteria in the quetiapine XR group were similar or lower than those for placebo. There was no

³ Per the AE page of the case report form.
⁴ Denominator is patients with <3 metabolic risk factors at baseline.
differential shift to any subcriteria of metabolic risk factors at end-of-treatment with quetiapine XR.

Overall, mean weight gain was higher in the quetiapine XR group (1.3 ± 3.7 kg) than placebo (-0.2 ± 2.3 kg). Weight gain of ≥7% at end-of-treatment was reported for 8.2% of quetiapine XR and 0.8% of placebo patients.

Quetiapine XR treatment is not associated with induction of mania or hypomania in bipolar I or II patients treated for acute bipolar depression. There were no AEs of treatment-emergent mania or hypomania. By YMRS mania criteria (score of ≥16 at 2 consecutive visits or at last visit), there was a slightly lower percentage of patients with YMRS-defined mania in the quetiapine XR group (4.4%) compared to the placebo group (6.4%).

In summary, quetiapine XR 300 mg is well-tolerated; there are no new safety findings.

Conclusion(s)

- Quetiapine XR 300 mg QD in the evening as monotherapy is superior to placebo in treatment of depression in patients with bipolar I and II disorder.
  - The antidepressant effect of quetiapine XR (300 mg QD) treatment was observed as early as 1 week following treatment initiation and was maintained throughout the 8-week treatment course in patients with bipolar I and II disorder who were experiencing a depressive episode.
  - Quetiapine XR 300 mg QD was effective in decreasing depressive symptoms in both rapid and non-rapid cyclers.
  - Quetiapine XR 300 mg QD was superior to placebo in achieving response (defined as MADRS total score at least 50% decrease from baseline) and remission (defined as MADRS score ≤12) in patients with bipolar I and II depression.

- Quetiapine XR, at a dose of 300 mg QD given in the evening was generally safe and well-tolerated in patients with bipolar I or II disorder who are experiencing a depressive episode.

Date of the report
13 Nov 2007
A Multicenter, Double-blind, Randomized, Parallel-group, Placebo-controlled, Phase III Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL®) Sustained-release as Monotherapy in Adult Patients with Acute Bipolar Mania

International co-ordinating investigator
Andrew Cutler, MD
Florida Research Center, LLC
3914 State Road
64 East
Bradenton, FL 34208

Study center(s)
This study was conducted at 50 centers in the United States; 48 sites actually enrolled patients.

Publications
None.

Study dates
First patient enrolled 22 December 2006
Last patient completed 31 July 2007

Phase of development
Therapeutic confirmatory (III)

Objectives
Primary objective
The primary objective was to demonstrate superior efficacy of quetiapine extended-release (XR)¹ formulation administered once daily (QD) as monotherapy at a dose of 400 to 800 mg

¹ Quetiapine XR was referred to as quetiapine sustained release (SR) in the protocol.
per day compared to placebo in decreasing the manic symptoms in patients with bipolar manic or mixed episode, after 3 weeks of treatment.

Secondary objectives

- To evaluate the efficacy and time course of quetiapine XR compared to placebo in decreasing the manic symptoms in patients with bipolar mania at each visit, including Day 4;

- To evaluate the efficacy of quetiapine XR compared to placebo in decreasing agitation and aggression in patients with bipolar mania;

- To evaluate the efficacy of quetiapine XR compared to placebo in decreasing psychotic symptoms in patients with bipolar mania;

- To evaluate the efficacy of quetiapine XR compared to placebo in decreasing depressive symptoms in patients with bipolar mania;

- To evaluate the safety and tolerability of quetiapine XR QD in patients with bipolar mania.

Study design

This was a 3-week, multicenter, randomized, parallel-group, double-blind, placebo-controlled, Phase III study of the efficacy and safety of quetiapine XR with flexible doses in the range of 400 to 800 mg or placebo given QD in the evening in the treatment of patients with bipolar I disorder with an acute manic episode. This study consisted of an enrollment period of up to 35 days and a 3-week treatment period with 1 of 2 treatment regimens (quetiapine XR 400 to 800 mg QD or placebo). Quetiapine XR was not down-titrated at the end of the study.

Target patient population

The per-protocol plan was to enroll approximately 447 patients, with approximately 313 randomized to receive study treatment to obtain 288 evaluable patients (ie, patients receiving at least 1 dose of investigational product who had at least 1 post-baseline Young Mania Rating Scale [YMRS] assessment).

Patients were male or female, 18 to 65 years of age, inclusive with a diagnosis of bipolar I disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Text Revision 4th Edition (DSM-IV-TR 2000) criteria of 296.4x (Bipolar I Disorder, Most Recent Episode Manic) or 296.6x (Bipolar I Disorder, Most Recent Episode Mixed) confirmed by the amended version of the Structured Clinical Interview for DSM-IV (SCID). Patients who experienced rapid cycling as defined in DSM-IV-TR were eligible to participate in the study.

To be enrolled in the study, patients must have had at least 1 bipolar manic or mixed episode in the prior 5 years, a YMRS total score at screening of ≥20 with a score of ≥4 on 2 of 4 of the following core YMRS items: irritability, speech, content, and disruptive/aggressive behavior;
and must have a Clinical Global Impression – Bipolar – Severity of Illness (CGI-BP-S) score of ≥4 on the overall bipolar illness item at randomization (Visit 2).

Both hospitalized and non-hospitalized patients were enrolled in the study. Patients were hospitalized at randomization and for at least the first 4 days of treatment.

**Investigational product and comparator(s): dosage, mode of administration and batch numbers**

Quetiapine XR was given at a dose of 300 mg (one 300-mg tablet) on Day 1 and at 600 mg (three 200-mg tablets) on Day 2. From Day 3 to Day 21, quetiapine XR was given in flexible doses of 400 to 800 mg (two to four 200-mg tablets). Quetiapine XR was orally administered QD, in the evening. Batch numbers used in this study were LA4600 (200-mg tablets) and LH 4708 (300-mg tablets).

**Comparator, dosage and mode of administration**

Placebo matching quetiapine XR 300-mg and 200-mg tablets was orally administered QD, in the evening. Batch numbers used in this study were CE889X (placebo matching quetiapine XR 200-mg tablets) and CE891X (placebo matching quetiapine XR 300-mg tablets).

**Duration of treatment**

Eligible patients had an up to 28-day washout period and an overall enrollment period of up to 35 days. Following the washout and enrollment period, patients were randomized and entered the 3-week treatment period.

**Criteria for evaluation (main variables)**

**Efficacy and pharmacokinetics**

- **Primary outcome variable:**
  - Change from baseline (randomization [Visit 2]) to final visit (Visit 6) in the YMRS total score.

- **Other variables supporting the primary objective:**
  - Change from baseline (randomization [Visit 2]) to final visit in YMRS total score response (patients with ≥50% reduction of YMRS);
  - YMRS total score remission (patients with a YMRS total score ≤12 at final visit [Visit 6]);
  - Change from baseline (randomization [Visit 2]) to final visit (Visit 6) Clinical Global Impression – Bipolar – Severity (CGI-BP-S);
  - Final visit (Visit 6) assessment in Clinical Global Impression – Bipolar – Change (CGI-BP-C);
- Proportion of patients at final visit (Visit 6) with a CGI-BP-C of “much improved” or “very much improved” in overall assessment.

  **Secondary outcome variables:**

  - Change from baseline (randomization [Visit 2]) to each visit (including Day 4) in the YMRS total score;

  - Score change from baseline (randomization [Visit 2]) to final visit (Visit 6) of Items 5 Irritability, or 9 Disruptive – Aggressive Behavior, of the YMRS;

  - Score change from baseline (randomization [Visit 2]) to final visit (Visit 6) of Item 8, Content (Thought Content) of the YMRS;

  - Change from baseline (randomization [Visit 2]) to final visit (Visit 6) of the Montgomery–Åsberg Depression Rating Scale (MADRS) total score.

**Safety**

- Change from baseline (defined as the sample/procedure taken closest to the randomization visit) in physical examinations, laboratory values (including glucose/lipids), vital signs, electrocardiogram (ECG);

- Adverse events (AEs), including somnolence, extrapyramidal symptoms (EPS) including akathisia, diabetes mellitus, QT prolongation, neutropenia/agranulocytosis, and suicidality;

- Serious adverse events (SAEs);

- Treatment-emergent EPS, as measured by the change in Simpson Angus Scale (SAS) total score and Barnes Akathisia Rating Scale (BARS) global assessment score from baseline (randomization [Visit 2]) to final visit (Visit 6) and AEs of EPS;

- Incidence of treatment-emergent depression (AE of depression or depressed mood, and or MADRS scores ≥18 on 2 consecutive assessments or on the final assessment);

- Proportion of patients withdrawing due to AEs;

- AEs leading to withdrawal;

- Change in weight from baseline (randomization [Visit 2]) to final visit (Visit 6);

- Proportion of patients with a ≥7% increase in weight from baseline (randomization [Visit 2]) to final visit (Visit 6);
- Incidences of suicidality using a suicidality classification similar to the one established by Columbia University.

**Statistical methods**

The power was set at 90% for a 2-sided test at $\alpha=0.05$ for the comparison between quetiapine XR and placebo, using a 5-unit difference from placebo (YMRS total score) with a pooled standard deviation of 13.

Efficacy analyses were based on the following patient populations, which were finalized before unblinding of the data.

- The modified intention-to-treat (MITT) analysis set (full analysis set) included all randomized patients who received at least 1 dose of study treatment and who had baseline (randomization [Visit 2]) values and at least one post-randomized YMRS assessment, classified by the randomized treatment assignment. Data from the MITT analysis set were used for analysis of the efficacy objectives.

- The per protocol (PP) analysis set, a subset of the MITT analysis set, included patients who had no major protocol violations or deviations affecting efficacy. Data from this population were used for a consistency check only for the analysis of the primary objective.

- The safety analysis set included all randomized patients who took $\geq 1$ dose of investigational product, classified according to the treatment actually received.

All statistical tests were 2-sided with a significance level of 5%, ie $\alpha=0.05$. Where appropriate, 95% confidence intervals are presented. Missing data resulting from patient withdrawal were imputed using a last observation carried forward (LOCF) approach. Patients with post-randomization data had their last study assessment carried forward as the final visit assessment for analysis. Also, descriptive statistics are provided for all variables.

**Patient population**

Baseline demographic and weight characteristics and patient disposition are shown in Table S1.
Table S1 Demographic and weight characteristics, and disposition (MITT population)

<table>
<thead>
<tr>
<th>Demographic or Baseline Characteristic</th>
<th>Quetiapine XR (N=149)</th>
<th>Placebo (N=159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>92 (61.7)</td>
<td>93 (58.5)</td>
</tr>
<tr>
<td>Female</td>
<td>57 (38.3)</td>
<td>66 (41.5)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>41.3 (10.3)</td>
<td>40.8 (10.7)</td>
</tr>
<tr>
<td>Median</td>
<td>42.0</td>
<td>43.0</td>
</tr>
<tr>
<td>Min, Max</td>
<td>19, 64</td>
<td>19, 63</td>
</tr>
<tr>
<td>Age category (years), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 - 39</td>
<td>61 (40.9)</td>
<td>65 (40.9)</td>
</tr>
<tr>
<td>40 - 65</td>
<td>88 (59.1)</td>
<td>94 (59.1)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>72 (48.3)</td>
<td>73 (45.9)</td>
</tr>
<tr>
<td>Black/ African American</td>
<td>70 (47.0)</td>
<td>77 (48.4)</td>
</tr>
<tr>
<td>American Indian/ Alaskan Native</td>
<td>3 (2.0)</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (0.7)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Native Hawaiian/ Pacific Islander</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (2.0)</td>
<td>7 (4.4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>91.8 (23.7)</td>
<td>91.0 (24.8)</td>
</tr>
<tr>
<td>Median</td>
<td>90.0</td>
<td>86.5</td>
</tr>
<tr>
<td>Min, max</td>
<td>48, 207</td>
<td>44, 189</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>149</td>
<td>156</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>100.0 (19.8)</td>
<td>100.0 (20.7)</td>
</tr>
<tr>
<td>Median</td>
<td>98.0</td>
<td>97.0</td>
</tr>
<tr>
<td>Min, max</td>
<td>66, 183</td>
<td>64, 183</td>
</tr>
</tbody>
</table>
### Table S1  Demographic and weight characteristics, and disposition (MITT population)

<table>
<thead>
<tr>
<th>Demographic or Baseline Characteristic</th>
<th>Quetiapine XR (N=149)</th>
<th>Placebo (N=159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>149</td>
<td>159</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>31.0 (9.0)</td>
<td>30.9 (8.2)</td>
</tr>
<tr>
<td>Median</td>
<td>29.3</td>
<td>28.8</td>
</tr>
<tr>
<td>Min, max</td>
<td>19, 78</td>
<td>17, 65</td>
</tr>
<tr>
<td>BMI category, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to &lt;18.5</td>
<td>0</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>18.5 to &lt;25</td>
<td>39 (26.2)</td>
<td>36 (22.6)</td>
</tr>
<tr>
<td>25 to &lt;30</td>
<td>37 (24.8)</td>
<td>47 (29.6)</td>
</tr>
<tr>
<td>30 to &lt;40</td>
<td>53 (35.6)</td>
<td>50 (31.4)</td>
</tr>
<tr>
<td>≥40</td>
<td>20 (13.4)</td>
<td>24 (15.1)</td>
</tr>
</tbody>
</table>

**Disposition**

- N (%) of patients who completed: 111 (71.6) for Quetiapine XR, 116 (72.0) for Placebo
- N (%) of patients who withdrew: 44 (28.4) for Quetiapine XR, 45 (28.0) for Placebo
- N analyzed for safety*: 151 (97.4) for Quetiapine XR, 160 (99.4) for Placebo
- N analyzed for efficacy (MITT): 149 (96.1) for Quetiapine XR, 159 (98.8) for Placebo
- N analyzed for efficacy (PP): 124 (80.0) for Quetiapine XR, 129 (80.1) for Placebo

*BMI Body mass index. MITT Modified intention-to-treat. n Number of patients. N Number of patients in treatment group. PP Per Protocol. SD Standard deviation. XR Extended-release.

*a Number of patients who received at least 1 dose of study drug.

Note: Denominators are N in treatment group by gender and characteristic.

In the MITT population, the 2 treatment groups were well matched with respect to age, race, and weight. Overall, a higher percentage of patients were male (60.1%) and the mean age was 41 years. Median weight and BMI were slightly lower in the placebo group compared to the quetiapine XR group (90.0 kg and 29.3 kg/m² for the quetiapine XR group and 86.5 kg and 28.8 kg/m² for the placebo group, respectively). By BMI category, there were more patients in the 25 to <30 kg/m² category for placebo (29.6%) than quetiapine XR (24.8%). The 30 to <40 kg/m² category had slightly more quetiapine XR patients (35.6%) than placebo patients (31.4%).

Baseline disease characteristics and psychiatric history are presented in Table S2.
<table>
<thead>
<tr>
<th>Baseline disease characteristics</th>
<th>Quetiapine XR (N=149)</th>
<th>Placebo (N=159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline YMRS score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>28.8 (5.4)</td>
<td>28.4 (5.1)</td>
</tr>
<tr>
<td>Min, max</td>
<td>20, 47</td>
<td>20, 47</td>
</tr>
<tr>
<td>Baseline CGI-BP-S depression score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>148</td>
<td>159</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.4 (1.2)</td>
<td>2.4 (1.2)</td>
</tr>
<tr>
<td>Min, max</td>
<td>1, 5</td>
<td>1, 5</td>
</tr>
<tr>
<td>Baseline CGI-BP-S mania score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>148</td>
<td>159</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>4.5 (0.7)</td>
<td>4.5 (0.7)</td>
</tr>
<tr>
<td>Min, max</td>
<td>4, 7</td>
<td>4, 7</td>
</tr>
<tr>
<td>Baseline CGI-BP-S overall bipolar illness score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>148</td>
<td>159</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>4.5 (0.7)</td>
<td>4.5 (0.7)</td>
</tr>
<tr>
<td>Min, max</td>
<td>4, 7</td>
<td>4, 7</td>
</tr>
<tr>
<td>Baseline MADRS score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>148</td>
<td>159</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>14.3 (7.0)</td>
<td>14.6 (6.4)</td>
</tr>
<tr>
<td>Min, max</td>
<td>0, 38</td>
<td>4, 34</td>
</tr>
<tr>
<td>Current episode, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manic</td>
<td>86 (57.7)</td>
<td>88 (55.3)</td>
</tr>
<tr>
<td>Mixed</td>
<td>63 (42.3)</td>
<td>71 (44.7)</td>
</tr>
<tr>
<td>Psychiatric history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid cycling*, n (%)</td>
<td>45 (30.2)</td>
<td>52 (32.7)</td>
</tr>
<tr>
<td>Years since bipolar diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Min, max</td>
<td>1.0, 50.0</td>
<td>2.0, 45.0</td>
</tr>
</tbody>
</table>
Table S2  
Baseline disease characteristics and psychiatric history (MITT population)

<table>
<thead>
<tr>
<th>Baseline disease characteristics</th>
<th>Quetiapine XR (N=149)</th>
<th>Placebo (N=159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of present mania episode (weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>146</td>
<td>154</td>
</tr>
<tr>
<td>Median</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Min, max</td>
<td>0.1, 29.7</td>
<td>0.1, 44.9</td>
</tr>
<tr>
<td>Attempted suicide, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>84 (56.4)</td>
<td>91 (57.2)</td>
</tr>
<tr>
<td>No</td>
<td>65 (43.6)</td>
<td>68 (42.8)</td>
</tr>
</tbody>
</table>

CGI-BP-S Clinical Global Impression – Bipolar -Severity of illness, MADRS Montgomery-Åsberg Depression Rating Scale. n Number of patients. N Number of patients in treatment group. SD Standard deviation. XR Extended-release. YMRS Young Mania Rating Scale.

a Defined as ≥4 and ≤8 mood episodes in the past year.

The 2 treatment groups were well-matched with respect to baseline disease characteristics. The majority of patients in both treatment groups had only manic episodes (versus mixed) at baseline (58% and 55% in the quetiapine XR and placebo groups, respectively); approximately 30% and 33% of patients in the quetiapine XR and placebo groups, respectively, had rapid cycling. Mean baseline YMRS scores were similar (28.8 and 28.4 for the quetiapine XR and placebo groups, respectively). Study patients in both treatment groups had greater severity of illness for mania in comparison with depression. The mean baseline CGI-BP-S score for mania was 4.5 in each treatment group and the mean CGI-BP-S score for depression was 2.4 in each treatment group. Mean baseline MADRS scores were also low at 14.3 (range 0 to 38) and 14.6 (range 4 to 34) for the quetiapine XR and placebo groups, respectively.

Efficacy results

Key efficacy results are presented for the MITT population in Table S3.

Table S3  
Key efficacy results (LOCF, MITT population)

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Quetiapine XR (N=149)</th>
<th>Placebo (N=159)</th>
<th>p-value at Day 4, Week 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>YMRS change, LS mean (SE)</td>
<td>Day 4</td>
<td>Week 3</td>
<td>Day 4</td>
</tr>
<tr>
<td></td>
<td>-9.89 (0.79)</td>
<td>-14.34 (0.91)</td>
<td>-6.87 (0.77)</td>
</tr>
<tr>
<td>Proportion with ≥50% YMRS response, n (%)</td>
<td>33 (22.6)</td>
<td>82 (55.0)</td>
<td>24 (15.2)</td>
</tr>
</tbody>
</table>
Table S3  Key efficacy results (LOCF, MITT population)

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Quetiapine XR (N=149)</th>
<th>Placebo (N=159)</th>
<th>p-value at Day 4, Week 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion with YMRS remission (total score &lt;=12), n (%)</td>
<td>Day 4 Week 3</td>
<td>Day 4 Week 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>27 (18.5) 62 (41.6)</td>
<td>20 (12.7) 44 (27.7)</td>
<td>0.112, 0.006</td>
</tr>
<tr>
<td>CGI-BP-S overall LS mean change from baseline (SE)</td>
<td>-0.81 (0.09) -1.51 (0.11)</td>
<td>-0.56 (0.09) -1.02 (0.11)</td>
<td>0.001, &lt;0.001</td>
</tr>
<tr>
<td>CGI-BP-C overall, LS mean (SE)</td>
<td>2.86 (0.09) 2.58 (0.12)</td>
<td>3.32 (0.09) 3.18 (0.12)</td>
<td>&lt;0.001, &lt;0.001</td>
</tr>
<tr>
<td>CGI-BP-C “much improved” or “very much improved”, n (%)</td>
<td>44 (30.1) 80 (53.7)</td>
<td>23 (14.6) 52 (32.7)</td>
<td>0.001, &lt;0.001</td>
</tr>
</tbody>
</table>


Quetiapine XR monotherapy at a dose of 400 to 800 mg QD for 3 weeks of treatment in patients with bipolar I mania (both manic and mixed at baseline) was superior to placebo in reducing the level of mania symptoms as measured by the change from baseline on the YMRS total score as early as Day 4 and continuing through the end of treatment (p≤0.003). The therapeutic effects of quetiapine XR were not restricted to any subgroup examined (gender, age group, race, manic/mixed episode, rapid/non-rapid cycling).

When analyzed by episode subgroup (patients with mixed versus only manic episodes at baseline), the MMRM results using OC data for the MITT population showed improvement in YMRS for both subgroups; the difference was statistically significant in favor of quetiapine XR over placebo for the manic subgroup (p≤0.001) but not for the mixed subgroup (p=0.107) at Week 3. The analysis by rapid cycling subgroups also showed improvement in YMRS for both subgroups; the difference was statistically significant in favor of quetiapine XR over placebo for the non-rapid cycling subgroup (p<0.001) but not for the rapid cycling subgroup (p=0.056).

Analysis of other secondary outcome variables also supported the superiority of quetiapine XR 400 to 800 mg QD over placebo in the treatment of mania in patients with bipolar disorder. The proportions of patients showing ≥50% reduction in YMRS total score (responders) and a YRMS total score ≤12 (remission) were statistically significantly higher for the quetiapine XR group compared to the placebo group by Day 8 (Week 1) and at the end of treatment (p≤0.024). The changes in CGI-BP-S and CGI-BP-C overall illness scores were statistically significant in favor of quetiapine XR beginning at Day 4 and continuing to the end of treatment (p≤0.011) with the exception of CGI-BP-C overall illness score at Day 15 (p=0.058). Quetiapine XR patients were 2.44 times more likely to have CGI-BP-C for overall
bipolar illness score of “much improved” or “very much improved” as placebo patients beginning at Day 4 and continuing to the end of treatment (p<0.001).

For the 4 key individual YMRS item scores used for eligibility criteria, including those related to secondary efficacy assessments (irritability, speech, thought content, and disruptive-aggressive behavior), all were reduced more by quetiapine XR treatment than by placebo treatment. Statistically significant separation from placebo was observed in the quetiapine XR group (p≤0.011) with the only exception being disruptive-aggressive behavior (p=0.063).

Quetiapine XR monotherapy at a dose of 400 to 800 mg QD for 3 weeks was also superior to placebo in decreasing depressive symptoms in patients with bipolar I mania as measured by the change from baseline in MADRS total score beginning at Day 4 and continuing to the end of treatment (p≤0.022).

Safety results

For patients treated with quetiapine XR, the mean daily dose over the treatment period was 603.8 mg with 47% of patients having a final dose level of 600 mg/day; approximately 22% and 29% of patients had final dose levels of 400 and 800 mg/day, respectively.

A summary of AEs is presented in Table S4.

Table S4  Overview of adverse events (safety population)

<table>
<thead>
<tr>
<th>AE category</th>
<th>Number (%) of patientsa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quetiapine XR (N=151)</td>
</tr>
<tr>
<td>Any AE</td>
<td>128 (84.8)</td>
</tr>
<tr>
<td>Any AE with an outcome of death</td>
<td>0</td>
</tr>
<tr>
<td>Any SAE</td>
<td>6 (4.0)</td>
</tr>
<tr>
<td>Any SAE leading to discontinuation of treatment</td>
<td>4 (2.6)</td>
</tr>
<tr>
<td>Any non-serious AE leading to discontinuation of treatment</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Any other significant AEb</td>
<td>0</td>
</tr>
</tbody>
</table>

AE Adverse event. N Number of patients in treatment group. SAE Serious adverse event. XR Extended-release.

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

b Any AE that led to dose of treatment being temporarily stopped, or deemed by the sponsor to be significant, excluding AEs reported as SAEs or led to discontinuation of treatment.

The percentage of patients with AEs was higher in the quetiapine XR (84.8%) than the placebo group (66.9%); however, the incidences of SAEs and discontinuations due to SAEs were higher in the placebo group (8.1% and 5.6%, respectively) compared with the quetiapine XR group (4.0% and 2.6%, respectively). The percentages of patients with discontinuation of
treatment due to non-serious AEs were comparable between the 2 treatment groups (2.0% in the quetiapine XR group and 2.5% in the placebo group). There was one “unexplained” death (placebo group).

The most common AEs were sedation, dry mouth, and somnolence, and all were reported more frequently in the quetiapine XR group (34.4%, 33.8%, and 16.6%, respectively) compared with placebo (7.5%, 6.9%, and 4.4%, respectively). Among AEs reported by >5% of patients in any group, AEs reported by at least twice as many patients in the quetiapine XR group compared to placebo included sedation, dry mouth, somnolence, constipation, dizziness, and weight increased.

Mean changes from baseline in glucose- and insulin-related laboratory variables were generally higher for the quetiapine XR-treated patients compared to placebo for patients both with and without diabetic risk factor(s) and for patients with diabetes mellitus; there was a large variability in results. For patients with diabetic risk factors at baseline, the incidence of clinically-important glucose values ≥100 and <126 mg/dL at Week 3 was lower in the quetiapine XR than the placebo group (46.4% vs. 54.4%); however, a greater percentage of patients in the quetiapine XR group had clinically-important glucose values ≥126 mg/dL compared with patients in the placebo group (10.1% vs. 4.4%). The incidence of clinically-important HbA1c values (>7.5%) was similar between the 2 treatments (4.3% and 2.9%). For patients with diabetes mellitus at baseline, the incidences of clinically-important glucose values ≥126 mg/dL and >200 mg/dL were also higher in the quetiapine XR group compared to the placebo group (57.1% vs. 33.3% and 28.6% vs. 0, respectively); none of these patients had clinically-important HbA1c values. A higher frequency of high glucose or HbA1c was not observed in patients with no diabetic risk factors at baseline.

Patients treated with quetiapine XR showed a slight mean increase in body weight consistent with findings of this treatment in other patient populations (1.3 kg for quetiapine XR and 0.1 kg for placebo). Increases in weight ≥7% were observed in 7 (5.1%) patients in the quetiapine XR group; no increases ≥7% occurred in placebo patients. There was no differential shift to ≥3 metabolic risk factors at end-of-treatment with quetiapine XR.

An increase in the incidence in the composite of AEs potentially related to EPS was noted for the quetiapine XR group compared with the placebo group (6.6% vs. 3.8%). The incidences of individual AEs potentially related to EPS were low in both treatment groups. No AEs were encoded to QT prolongation. There were no AEs potentially related to neutropenia/agranulocytosis during the study; however, clinically laboratory assessments showed that 3 patients (2 quetiapine XR and 1 placebo) had shifts in neutrophil values from non-clinically significant at baseline to clinically-important low values (<1.5 x 10⁹/L) at the end of treatment.

Treatment-emergent depression, as defined by criterion of MADRS and AEs relating to depression, was reported for 1 patient in the placebo group. Patients in the placebo group showed a slightly higher incidence of suicidal behavior/ideation and possible suicidal
behavior/ideation than patients treated with quetiapine XR (3.1% in the placebo group vs. 1.3% in the quetiapine XR group).

**Conclusion(s)**

- Quetiapine XR 400 to 800 mg given QD in the evening for 3 weeks, flexibly dosed, as monotherapy is superior to placebo in treatment of mania in patients with bipolar I diagnosis.
  - The effect of quetiapine XR (400 to 800 mg QD) treatment in decreasing manic symptoms was observed as early as Day 4 following treatment initiation and was maintained throughout the 3-week treatment course in patients with bipolar disorder.
  - Quetiapine XR 400 to 800 mg given QD was effective in decreasing manic symptoms in patients exhibiting either rapid or non-rapid cycling.
  - Quetiapine XR 400 to 800 mg given QD was superior to placebo in achieving response (defined as ≥50% reduction of YMRS) and remission (defined as YMRS score ≤12) in patients with bipolar mania.

- Quetiapine XR, at a dose of 400 to 800 mg given QD, flexibly dosed, was generally safe and well-tolerated in patients with bipolar disorder who were experiencing a manic episode.

**Date of the report**

20 November 2007
Attachment 3
Curriculum Vitae

Please fill in this form in English

First and Family Name
Vikram Mehra, MD

Date of birth (dd/mm/yyyy)
29/04/1967

Present appointment
Investigator

(Job title/Department)

Address
R&D Clinical Research, Inc.
10101 Southwest Fwy., Ste. 340, Houston, TX 77074

(Full work address including post/zip code)

Qualifications
MD, Year: MD, 1993
Specialist, Field: Board Certified, Year: 1998
Psychiatry

(Degree and other professional qualifications)

(✓ relevant qualifications, or specify)

PhD ☐ MSc ☐ BSc ☐

Other

(specify)

Physician's reference/licence number
Texas #J6591

(if applicable)

Previous appointments/experience
May 2002 – Present Private Practice, 10101 S.W. Fwy.,
St. 310, Houston, TX 77074
2001-Present R&D Clinical Research, 461 This
Way, Lake Jackson, TX 77566
July 2003 – Present Medical Director, Adult Unit, West
Oaks Hospital, Houston, TX
Apr. 2002 – Aug. 2002 Medical Director, Geriatric Unit,
Kingwood Health Center, Kingwood, TX
Oct. 2000-Jan. 2003 TriCounty Mental Health/Mental
Retardation (TCMHR) Conroe, TX
Counseling Center, Tomball, TX
Sept.2000-Apr. 2002 Medical Director Inpatient Unit,
New Day Counseling Center, Tomball, TX
of North Houston, Inc., Kingwood, TX

(include only relevant therapeutic/practical
experience after gaining qualifications)
Publications (✓ appropriate box)  
(Number of articles published)

Previous experience in clinical trials and type of GCP training received  
(eg. 3 trials in the cardiovascular field and 2 in the respiratory field, GCP training at investigators meetings for 3 of these studies)

Sept. 1998-Jun. 1999 Medical Director-Geriatric Unit  
Charter Hospital, Kingwood, TX

☐ 0  1-5  ✓ 6-10  ☐ 11-20  ☐ >20  ☐

Dr. Mehra has been involved as a Sub-Investigator/Principal Investigator with 5+ years of clinical trial experience during which time he has participated in excess of 75+ trials over several therapeutic areas including studies such as: ADHD, Insomnia, General Anxiety, Social Anxiety Disorder, Depression, Panic, Bipolar, Obesity, Osteoarthritis, Ankle Sprain, Dyspepsia, GERD, Sinephritis, Neuropathy, Hypertension, Migraine, Bronchitis, Pneumonia, Alzheimer’s, Diabetes, Low Back Pain, etc. He has received training/certification for the following psychiatric evaluations: MINI, SKID, SIGHA, ISAS, SNRI, SSRI, MADRAS, HAMD, HAMA, ADHDRS, ACDS, BECK Suicide

GCP training provided at investigators meetings

Date of signature  
5/2/2000

Signature  
[Signature]
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Doris Bates
2/7/2008 05:04:41 PM
Inspection requested to support S006 and S007. S008 is considered to be supported by inference from the data submitted under S007; a separate inspection is not required for S008.

Thomas Laughren
2/8/2008 08:30:22 AM
MEMORANDUM

CLINICAL INSPECTION SUMMARY

DATE: September 19, 2008

TO: Doris Bates, Regulatory Project Manager
    Cara Alfaro, Clinical Reviewer
    Division of Psychiatry Products

FROM: John Lee, Medical Officer
      Good Clinical Practice Branch II
      Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, MD
          Branch Chief, Good Clinical Practice Branch II
          Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 22-047 SE 6/7

APPLICANT: AstraZeneca

DRUG: Quetiapine Fumarate Extended Release Tablets (Seroquel XR)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: Treatment of Bipolar Disorder

CONSULTATION REQUEST DATE: February 6, 2008

DIVISION ACTION GOAL DATE: September 19, 2008

PDUFA DATE: October 19, 2008
I. BACKGROUND

Bipolar disorder

Bipolar I disorder is characterized by one or more manic (or mixed) episodes, usually alternating with major depressive episodes. Bipolar II disorder is characterized by one or more major depressive episodes and at least one hypomanic episode. Bipolar depression refers to the major depressive episodes that occur with bipolar I and II disorders. Patients with bipolar disorder are often misdiagnosed as having a unipolar depressive disorder until they experience a manic or hypomanic episode.

The lifetime prevalence of bipolar disorders in the United States (US) has been estimated to be about 4%, evenly divided between men and women. Even with treatment, bipolar patients are often symptomatic, more often with depressive than with manic symptoms. Mortality is high among bipolar patients (increased risk-taking behavior, other coexisting psychiatric illnesses, suicide). The risk of suicide among bipolar patients is over 20-fold higher than the general population (0.4% vs 0.017% per year).

Quetiapine fumarate (Seroquel)

The use of antidepressants as monotherapy is generally not recommended for bipolar depression since patients may switch into hypomania or mania from depression or experience cycle acceleration. This risk may be mitigated by combining an antidepressant with a mood stabilizing agent (lithium, divalproex), but combination therapies are often limited in their efficacy, are subject to more adverse reactions than with a single agent, and typically result in reduced patient compliance. For lithium and divalproex, the need for laboratory tests to monitor a relatively narrow therapeutic index is often treatment-limiting.

Monotherapy using quetiapine fumarate (Seroquel), a dibenzothiazepine derivative, has been shown to be effective in improving symptoms of bipolar depression with little risk of conversion to hypomania or mania. Quetiapine is not a new molecular entity (NME) and has been previously approved in the US for the treatment of schizophrenia and bipolar disorder, as follows:

- Quetiapine immediate-release (IR)
  - Schizophrenia, 1997
  - Mania associated with bipolar disorder, 2003
  - Depression associated with bipolar disorder, 2006

- Quetiapine sustained-release (SR)
  - Schizophrenia, 2007
  - Mania associated with bipolar disorder (NDA 22-047 currently under review)
  - Depression associated with bipolar disorder (NDA 22-047 currently under review)

The pharmacokinetic profile of quetiapine SR is more constant (less extreme peak/trough drug concentrations) than that of the older IR formulation. The relationship between the more constant PK profile of the SR formulation and its clinical efficacy and safety in bipolar disorder has not been demonstrated. In proposing to expand its clinical indication to include the bipolar indication (current NDA efficacy supplements 6 and 7), the sponsor provides controlled data relative to placebo.
Study Protocols

Two pivotal studies support this NDA. Study D144CC00002 was a multicenter, double-blinded, randomized, parallel-group, placebo-controlled study of the efficacy and safety of Seroquel XR in adults with acute bipolar depression. In this study of approximately 270 subjects treated for 8 weeks, test and control groups were compared for the change from baseline in MADRS (Montgomery-Asberg Depression Rating Scale) score. Study D144CC00004 was similar to Study D144CC00002 but was conducted in approximately 290 subjects with acute bipolar mania using a briefer (3 weeks) treatment period and YMRS (Young Mania Rating Scale) score as the primary outcome variable.

One clinical site (Dr. Vikram Mehra) was selected for audit, due to reasonably high enrollment and the fact that he was involved with both pivotal studies.

II. INSPECTION RESULTS

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>Protocol Subjects</th>
<th>Inspection Dates</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vikram Mehra, MD</td>
<td>D144CC00002 20 enrolled 12 randomized</td>
<td>8/11 - 8/13 2008</td>
<td>NAI pending</td>
</tr>
<tr>
<td>RD Clinical Research, Inc.</td>
<td>D144CC00004 33 enrolled 12 randomized</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10101 Southwest Freeway, Suite 340</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Houston, TX 77074</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NAI = no action indicated (no deviations from regulations); VAI = voluntary action indicated (no significant deviations from regulations); OAI = official action indicated (significant deviations from regulations); NA = not applicable

Classification:
Field = field investigator's initial recommendation in classifying the inspection result
Final = CDER's final classification of the inspection result

Vikram Mehra, MD: NAI

RD Clinical Research, Inc.
10101 Southwest Freeway, Suite 340
Houston, TX 77074

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, adherence to protocol and applicable regulations.

- Data verification: primary efficacy endpoint data, adverse events, concomitant medication use, protocol violations, and subject discontinuation

- Subjects:
  o D144CC00002: 20 subjects were screened, 13 enrolled, and 9 completed the study.
    Complete records were reviewed for all subjects enrolled.
D144CC00004: 13 subjects were screened, 12 enrolled, and 10 completed the study. Complete records were reviewed for all subjects enrolled.

b. General observations and commentary: No significant deficiencies were observed and a Form FDA 483 was not issued. Both studies (D144CC00002 and D144CC00002) were conducted in compliance with applicable Good Clinical Practice (GCP) regulations and respective study protocols. Study monitoring including IRB oversight was adequate.

c. Assessment of data integrity: The data from both studies appear reliable.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

No significant deficiencies were observed at this inspection. A Form FDA 483 was not issued for either study (D144CC00002 and D144CC00002). The data generated from this site are considered acceptable in support of the proposed indications.

Note: The final inspection report is pending as of September 17, 2008. Upon receipt and review of the final inspection report, an addendum to this clinical inspection summary will be provided if additional observations of clinical or regulatory significance are discovered.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Lee
9/22/2008 04:28:32 PM
MEDICAL OFFICER

Tejashri Purohit-Sheth
9/22/2008 04:54:20 PM
MEDICAL OFFICER
NDA REGULATORY FILING CHECKLIST

NDA # 22047  Efficacy Supplement Type SE- SE1 Supplement # 006
" " " " "  " " 007
" " " " "  " " 008

Proprietary Name, Established Name: Seroquel XR (quetiapine fumarate) Tablets
Dosage Form, Strengths: Tablets, 50, 200, 300, 400 mg
Indication(s) requested:

S006: use of quetiapine as monotherapy in the treatment of bipolar depression.
S007: use of quetiapine as monotherapy in the treatment of bipolar mania.
S008: use of quetiapine as adjunctive therapy in the treatment of bipolar mania.

All three supplements submitted in one electronic submission on same date.

Applicant: AstraZeneca UK, Ltd.
Agent for Applicant (if applicable): AstraZeneca Pharmaceuticals LP

Date of Application: 19DEC07  Date of Receipt: 19DEC07  Clock started: 19DEC07
Filing Meeting: 30JAN08  Filing Date: 17FEB08  Day 74: 02MAR08
Midcycle: 19MAY08  Month 8: 19AUG08  UF Goal Date: 19OCT08

List referenced IND numbers:

Type of Original NDA:
AND (if applicable)
Type of Supplement:
Review Classification: S X P
Resubmission after withdrawal?
Chemical Classification: (1,2,3 etc.) 3

Form 3397 (User Fec Cover Sheet) submitted: YES X
S-006 and 007
User Fee Status: Paid X Exempt (orphan, government) Waived (e.g., small business, public health)

Is the application affected by the Application Integrity Policy (AIP)?
If yes, explain:
If yes, has OC/DMPQ been notified of the submission?
Does the submission contain an accurate comprehensive index?
Was form 356h included with an authorized signature for the submission?
Is the submission complete as required under 21 CFR 314.50?

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars', click on 'Forms'. On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.
Background: S-006, S-007, and S-008 provide for the use of quetiapine extended release tablets to treat bipolar depression, and as monotherapy and adjunctive therapy with lithium or [80] for bipolar disorder, manic or mixed.

Quetiapine XL was approved on May 15, 2007 for the acute treatment of schizophrenia, and on November 15, 2007 for the maintenance treatment of schizophrenia. On November 2, 2007, the Division sent AZ preliminary comments for an end of Phase 2 meeting for this dosage form in the bipolar indication. AZ canceled the formal meeting, based on the preliminary comments. No pre-submission meeting was requested or held, and the subject supplements were received by the Agency on December 19, 2007.

Note that S-008 is a putative claim for adjunctive therapy based not on clinical data but on extrapolation from a purportedly positive monotherapy study in conjunction with the existing approval of adjunctive therapy for the immediate release dosage form. However, a User Fee has been paid.

Note also the inclusion of the 50 mg tablet strength in this submission. See CMC below for details.

Meeting Details:

Per reviewers, are all parts in English or English translation? YES X NO

CLINICAL FILE X REFUSE TO FILE
- Clinical site inspection needed?
- Domestic or foreign? Domestic X Foreign

A domestic inspection will be requested at a single site which supported all submissions.
- Advisory Committee Meeting needed? YES, date if known NO X
- Is application affected by AIP N/A X YES NO
- Has Division made a recommendation regarding exception to the AIP to permit review based on medical necessity or public health significance?
- Clinical Questions for 74-Day Letter? N/A X YES NO

CLINICAL MICROBIOLOGY N/A X FILE REFUSE TO FILE

STATISTICS N/A FILE X REFUSE TO FILE
- Questions for 74-Day Letter? YES -- questions from statistical team were provided at this meeting.

CLINICAL PHARMACOLOGY N/A X FILE REFUSE TO FILE
- Biopharm. inspection needed?
- Domestic or foreign? Domestic Foreign

NONCLINICAL PHARMACOLOGY N/A FILE REFUSE TO FILE
- Receptor-related information in Section 12 of reformatted label requires nonclinical pharmacology review. However, this is not related to a filing decision.

CMC N/A FILE X REFUSE TO FILE
- Applicant is proposing to introduce a previously approved but not marketed 50 mg strength. This strength was approved with the initial NDA but no labeling was associated with it. The container labels have been requested and provided.

ELECTRONIC SUBMISSION: Yes
Any comments: S-008 was created administratively by FDA to support the bundled adjunctive therapy claim made along with the monotherapy claim in S-007. A User Fee was paid for this claim.

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

S-006       The application, on its face, appears to be sufficiently well-organized and indexed to permit filing.
S-007       This decision does not guarantee that no deficiencies will be identified during review. It also does not guarantee a first cycle approval action.
S-008       No filing issues identified.
             X   Filing issues to be communicated by Day 74

COMMENTS / ACTION ITEMS:

74-day letter to issue by 02MAR2008.

Doris J. Bates, Ph.D.
Regulatory Project Manager, HFD-130
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Doris Bates
7/10/2008 03:49:33 PM